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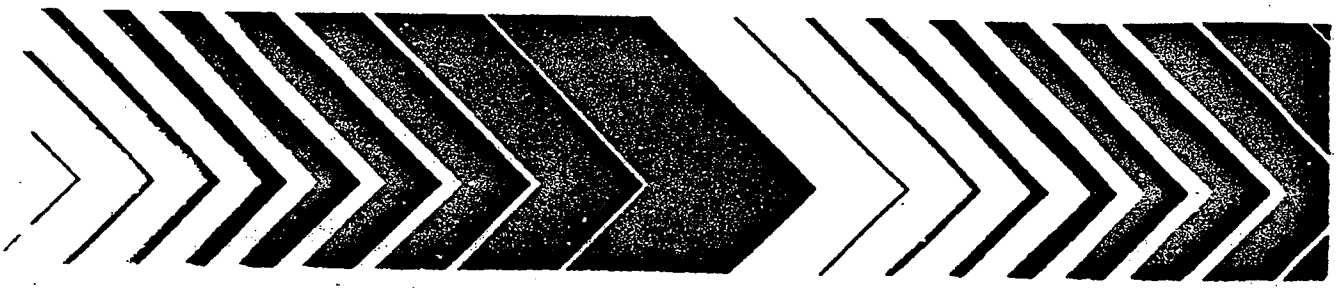

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Airborne Asbestos Health Assessment Update

Environmental Criteria and Assessment Office
Office of Health and Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Research Triangle Park, N.C. 27711

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PREFACE

This Asbestos Health Assessment Update document has been prepared by the Environmental Criteria and Assessment Office of the U.S. Environmental Protection Agency (EPA), Office of Health and Environmental Assessment (OHEA). The document was developed to serve as the scientific basis for EPA review and revision, as appropriate, of the National Emission Standards for Asbestos as a hazardous air pollutant.

The document was reviewed and critiqued in July, 1984, by the Environmental Health Committee (EHC) of the U.S. EPA Science Advisory Board (SAB) and subsequently revised to take into account the peer-review comments of that SAB committee. The Science Advisory Board provides advice on scientific matters to the Administrator of the U.S. Environmental Protection Agency.

In the development of this assessment document, pertinent scientific literature has been critically evaluated and conclusions are presented in such a manner that the toxicity of asbestos and related characteristics are identified. Estimates of the fractional increased risk of lung cancer and mesothelioma per unit exposure of asbestos are also discussed, in an attempt to quantify adverse health effects associated with exposure to asbestos via inhalation.

ABSTRACT

Data developed since the early 1970s, from large population studies with long follow-up, have added to our knowledge of asbestos-related diseases and strengthened the evidence for associations between asbestos and specific types of health effects. Lung cancer and mesothelioma are the most important asbestos-related causes of death among exposed individuals. Cancer at other sites also has been associated with asbestos exposure. The accumulated data suggest that the excess risk of lung cancer from asbestos exposure is proportional to the cumulative exposure (the duration times the intensity) and the underlying risk in the absence of exposure. The risk of death from mesothelioma is approximately proportional to the cumulative exposure to asbestos and increases sharply with time since onset of exposure. Animal studies confirm the human epidemiological results and indicate that all major asbestos varieties produce lung cancer and mesothelioma, with only limited differences in carcinogenic potency. Some measurements demonstrate that asbestos exposures exceeding 100 times background occur in non-occupational environments. Currently, the most important of these non-occupational exposures is the release of fibers from asbestos-containing surfacing materials in schools, auditoriums, and other public buildings, or from sprayed asbestos fireproofing in high-rise office buildings. Extrapolations of risks of asbestos cancers from occupational circumstances can be made, although numerical estimates in a specific exposure circumstance have a large (approximately tenfold) uncertainty. Because of this uncertainty, calculations of unit risk values for asbestos at low concentrations must be viewed with caution. They are subjective, to some extent, and are also subject to the following limitations in data: 1) variability in the exposure-response relationship at high exposures; 2) uncertainty in extrapolating to exposures 1/100 as much; and 3) uncertainties in conversion of optical fiber counts to electron microscopic fiber counts or mass determinations.

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1. SUMMARY

Data developed since the early 1970s, from large population studies with long follow-up, have added to our knowledge of asbestos disease. These data strengthen and quantitatively define the association of asbestos exposure with disease. Lung cancer and mesothelioma are the most important asbestos-related causes of death among exposed individuals. Gastrointestinal cancers are also increased in most studies of occupationally exposed workers. Cancer at other sites (larynx, kidney, ovary) has also been shown to be associated with asbestos exposure in some studies, but the degree of excess risk and the strength of the association are less for these and the gastrointestinal cancers than for lung cancer or mesothelioma. The International Agency for Research on Cancer (1982) lists asbestos as a group 1 carcinogen, meaning that exposure to asbestos is carcinogenic to humans. EPA's proposed guidelines would categorize asbestos as Group A, human carcinogen (Federal Register, 1984b).

Data from a study of U.S. insulation workers allow models to be developed for the time and age dependence of lung cancer and mesothelioma risk. Thirteen other studies provide exposure-response information. The accumulated data suggest that the excess risk of death from lung cancer from asbestos exposure is proportional to the cumulative exposure (the duration times the intensity) and the underlying risk in the absence of exposure. The time course of lung cancer is determined primarily by the time course of the underlying risk. However, the risk of death from mesothelioma increases very rapidly after the onset of exposure and is independent of age and cigarette smoking. As with lung cancer, the risk appears to be proportional to the cumulative exposure to asbestos in a given period. The dose and time relationships for other asbestos cancers are uncertain.

Fourteen studies provide data for a best estimate fractional increased risk of lung cancer per unit exposure. The values characterizing the lung cancer risk obtained from different studies vary widely. Some of the variability can be attributed to specific processes. Chrysotile mining and milling, and perhaps friction product manufacture, appear to have lower unit exposure risks than chrysotile textile production and other uses of asbestos. Other variability can be associated with the uncertainties of small numbers in epidemiological studies and misestimates of the exposures of earlier years. Finally, some differences between studies may be related to differences in

fiber type, but these are much less than those associated with specific processes.

Four studies provide similar quantitative data on the unit exposure risk for mesothelioma and six additional studies provide corroborative, but less accurate, quantitative data. The same factors that affect the lung cancer unit exposure risk appear to affect that of mesothelioma as the ratio of a measure of mesothelioma risk to excess lung cancer risk is roughly constant across the ten studies. However, in other studies the ratio of number of mesothelioma deaths to lung cancer deaths among groups exposed to substantial quantities of crocidolite is two to four times higher than among groups exposed predominantly to other fibers. Further, the risk of peritoneal mesothelioma appears to be less from exposure to chrysotile than to either crocidolite or amosite, but this suggestion is tempered by uncertainties associated with the greater possibility of misdiagnosis of the disease.

Animal studies confirm the human epidemiological results. All major asbestos varieties produce lung cancer and mesothelioma with only limited differences in carcinogenic potency. Implantation and injection studies show that fiber dimensionality, not chemistry, is the most important factor in fiber-induced carcinogenicity. Long (>4 μm) and thin (<1 μm) fibers are the most carcinogenic at a cancer-inducible site. However, the size dependence of the deposition and migration of fibers also affects their carcinogenic action in humans.

Measurements demonstrate that asbestos exposures exceeding 100 times the background occur to individuals in some non-occupational settings. Currently, the most important of these non-occupational exposures is from the release of fibers from asbestos-containing surfacing materials in schools, auditoriums, and other public buildings, or from sprayed asbestos-containing fireproofing in high-rise office buildings. A high potential exists for future exposure from the maintenance, repair, and removal of these materials.

Extrapolations of risks of asbestos cancers from occupational circumstances can be made, although numerical estimates in a specific exposure circumstance have a large (approximately tenfold) uncertainty. Because of this uncertainty, calculations of unit risk values for asbestos at the low concentrations measured in the environment must be viewed with caution. The best estimate of risk to the United States general population for a lifetime continuous exposure to 0.0001 f/ml is 2.8 mesothelioma deaths and 0.5 excess lung cancer deaths per 100,000 females. Corresponding numbers for males are

1.9 mesothelioma deaths and 1.7 excess lung cancer deaths per 100,000 individuals. Excess GI cancer mortality is approximately 10-30 percent that of excess lung cancer mortality. These risks are subjective, to some extent, and are also subject to the following limitations in data: 1) variability in the exposure-response relationship at high exposures; 2) uncertainty in extrapolating to exposures 1/100 as much; and 3) uncertainties in conversion of optical fiber counts to electron microscopic fiber counts or mass determinations.

Recently several government agencies in different countries reviewed asbestos health effects. Areas of agreement and disagreement between these other reviews and those of this document are presented. A comparison of the different risk estimates is provided.

2. INTRODUCTION

The principal objective of this "Airborne Asbestos Health Assessment Update" document is to provide the U.S. Environmental Protection Agency (EPA) with a sound scientific basis for review and revision, as appropriate, of the national emission standard for asbestos, 40 CFR 61, subpart B, as required by the 1977 Clean Air Act Amendments, Sections 111 and 112. The health effects basis for designating asbestos as a hazardous pollutant and minimizing emissions via the original 1973 National Emissions Standard for Hazardous Air Pollutants (NESHAP) was scrutinized, at that time, during two public hearings and a public comment period. Once a pollutant has been designated as a "hazardous" air pollutant, the burden of proof is placed on proving that designation wrong. The original health effects basis for designating asbestos as a hazardous air pollutant was qualitative evidence establishing asbestos-associated carcinogenic effects. However, insufficient bases then existed by which to define pertinent quantitative dose-response relationships; i.e., unit risk values could not be credibly estimated. The main focus of this update document is to describe asbestos-related health effects developments since 1972, and to determine if new data warrant the specification of unit risk values for asbestos. This report forms part of the basis to perform a risk assessment. The National Academy of Sciences (NAS) in 1983 suggested a definition of risk assessment as the use of the factual data base to define the health effects of exposure of individuals or populations to hazardous materials, such as asbestos in this case (National Academy of Sciences, 1983). This update document is not meant to characterize the status of asbestos measurement techniques or mineralogical characterization, although they are presented briefly as background information. Because this document is concerned only with the excess risk of cancer from inhalation of asbestos fibers, consideration of the risk posed from ingesting asbestos fibers also is outside its scope. A separate criteria document for asbestos in water is being prepared by the EPA.

Thus, emphasis is placed on the literature published after 1972 and on those papers that provide information on the risk from low-level exposures, such as those encountered in the non-occupational environment. Specifically, this report addresses the following issues:

1. Are there models that illustrate the age, time, and exposure dependence of asbestos diseases that can be used satisfactorily in a quantitative risk assessment?

2. Is there consistency among studies and sufficiently good estimates of exposure in occupational circumstances so that useful exposure-response relationships can be established?

3. Do these studies indicate any significant differences in the carcinogenic potency of different asbestos minerals or of fibers of different dimensionality?

4. What additional or confirmatory information relating to human carcinogenicity is provided by animal studies?

5. What are the non-occupational concentrations of asbestos to which populations are exposed?

6. Is there a basis for making numerical estimates of risks of asbestos disease that might result from non-occupational exposures?

Two documents provide good reviews of the status of knowledge of the health effects of asbestos in the early 1970s. One is the criteria document for occupational exposure to asbestos produced by the National Institute of Occupational Safety and Health as part of the Occupational Safety and Health Administration's consideration of an asbestos standard in early 1972 (National Institute for Occupational Safety and Health, 1972). The second is the proceedings of a conference sponsored by the International Agency for Research on Cancer (IARC), which was convened in October 1972 with the stated purpose of reviewing the knowledge of the biological effects of asbestos (Bogovski et al., 1973), and included a report by an Advisory Committee on Asbestos Cancers appointed by the IARC to review evidence relating exposures to asbestos dust to cancers.

2.1 SUMMARY OF ASBESTOS HEALTH EFFECTS THROUGH 1972

This section relies heavily on review articles found in the proceedings of the October 1972 IARC meeting and in the report of the IARC Advisory Committee published therein (Bogovski et al., 1973) for a summary of health effects knowledge as of 1973.

2.1.1 Occupational Exposure

Diseases considered to be associated with asbestos exposure in 1972 included asbestosis, mesothelioma, bronchogenic carcinoma, and cancers of the gastrointestinal (GI) tract, including the esophagus, stomach, colon, and rectum. Lung cancer was associated with exposure to all principal commercial varieties of asbestos fiber: amosite, anthophyllite, crocidolite, and chrysotile. Excess risks of bronchogenic carcinoma were documented in mining and milling, manufacturing, and end product use (application of insulation materials). Mesothelioma was a cause of death among factory employees, insulation applicators, and workmen employed in the mining and milling of crocidolite. A much lower risk of death from mesothelioma was observed among chrysotile or amosite mine and mill employees, and no cases were associated with anthophyllite exposure. The IARC Advisory Committee suggested that the risk of death from mesothelioma was greatest with crocidolite, less with amosite, and still less with chrysotile. This suggestion was based on the association of disease with exposures. No unit exposure risk information existed.

Information on exposure-response relationships for lung cancer risk among various exposed groups was scanty. Data from Canadian mine and mill employees clearly indicated an increasing risk with increasing exposure, measured in terms of millions of particles per cubic foot-years (mppcf-y), but data on the risk at minimal exposure were uncertain because the number of expected deaths calculated using adjacent county rates suggested that all exposure categories were at elevated risk (McDonald et al., 1971). A study of retirees of the largest U.S. asbestos manufacturer showed lung cancer risks ranging from 1.7 times that expected in the lowest exposure category to 5.6 times that expected in the highest (Enterline and Henderson, 1973). Exposures were expressed in mppcf-y and information on conversion of mppcf to fibers per milliliter was available only for textile production. Despite the paucity of data, the report of the Advisory Committee on Asbestos Cancers to the IARC (Bogovski et al., 1973) stated, "The evidence ... suggests that an excess lung carcinoma risk is not detectable when the occupational exposure has been low. These low

occupational exposures have almost certainly been much greater than that to the public from general air pollution." Limited data existed on the association of GI cancer with asbestos exposure, but the "excess is relatively small compared with that for bronchial cancer."

The prevalence of asbestosis, particularly as manifested by X-ray abnormalities of the pleura or parenchymal tissue, had been documented more extensively than the risk of the asbestos-related malignancies. In part, this documentation resulted from knowledge of this disease extending back to the turn of the century, whereas the malignant potential of asbestos was not suggested until 1935 (Lynch and Smith, 1935; Gloyne, 1936) and not widely appreciated until the 1940s (Merewether, 1949). Asbestosis had been documented in a wide variety of work circumstances and associated with all commercial types of asbestos fibers. Among some heavily exposed groups, 50 to 80 percent of individuals employed for 20 or more years were found to have abnormal X-rays characteristic of asbestos exposure (Selikoff et al., 1965; Lewinsohn, 1972). A lower percentage of abnormal X-rays was present in lesser exposed groups. Company data supplied to the British Occupational Hygiene Society (British Occupational Hygiene Society, 1968) on X-ray and clinical abnormalities among 290 employees of a large textile production facility in Great Britain were analyzed by Berry (1973) in terms of a fiber exposure-response relationship. The results were utilized in establishing the 1969 British regulation on asbestos. These data, shown in Figure 2-1, suggested that the risk of developing the earliest signs of asbestosis (rales) was less than 1 percent for accumulated fiber exposure of 100 fiber-years/ml (f-y/ml), e.g., 2 fibers/milliliter (f/ml) for 50 years. However, shortly after the establishment of the British Standard, additional data from the same factory population suggested a much greater prevalance of X-ray abnormalities than was believed to exist at the time the British Standard was set (Lewinsohn, 1972). These data resulted from use of the new International Labour Office (ILO) U/C standard classification of X-rays (International Labour Office, 1971) and the longer time from onset of employment. Of the 290 employees whose clinical data were reviewed by the BOHS, only 13 had been employed for 30 or more years; 172 had less than 20 years of employment. The progression of asbestosis depends on both cumulative exposure and time from exposure; therefore, analysis in terms of only one variable (as in Figure 2-1) can be misleading.

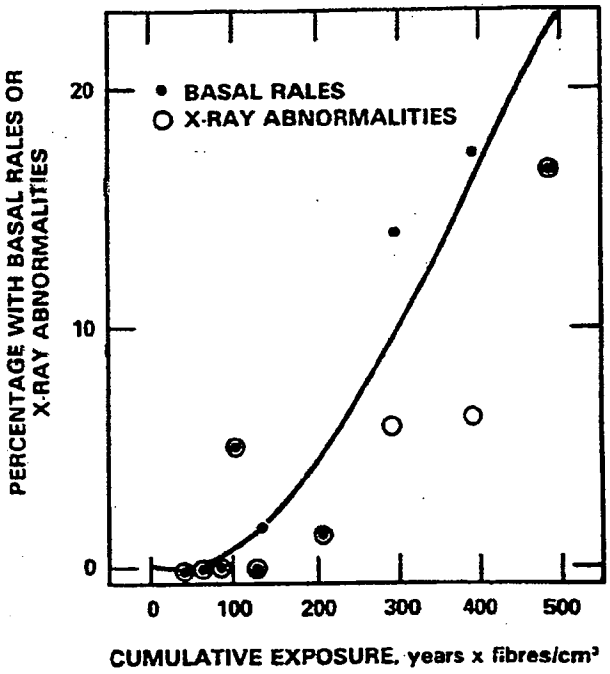

Figure 2-1. Dose-response relationship for prevalence of basal rales in a chrysotile asbestos factory.

Source: Berry (1973); x-ray data added from British Occupational Hygiene Society (1968).

2.1.2 Environmental and Indirect Occupational Exposure Circumstances

Several research groups had shown that asbestos disease risk could develop from other than direct occupational exposures. Wagner, Sleggs, and Marchand (1960) showed that a mesothelioma risk in environmental circumstances existed in the mining areas of the Northwest Cape Province of South Africa. Of 33 mesotheliomas reported over a 5-year period, roughly half were from occupational exposure. However, all but one of the remainder resulted from exposure occasioned by living or working in the area of the mining activity. A second study that showed an extra-occupational risk was that of Newhouse and Thompson (1965) who investigated the occupational and residential background of 76 individuals deceased of mesothelioma in the London hospital. Forty-five of the decedents had been employed in an asbestos industry; of the remaining 31, 9 lived with someone employed in asbestos work and 11 were individuals who resided within half a mile of an asbestos factory. Bohlig and Hain (1973) identified environmental asbestos exposure in 38 mesothelioma cases without occupational exposure who resided near an asbestos factory, further defining residential risk. A final study, which is particularly important because of the size of the population implied to be at risk, was that of Harries (1968), who pointed to a risk of asbestos disease from indirect occupational exposure in the shipbuilding industry. He described the presence of asbestosis in 13 individuals and mesothelioma in 5 others who were employed in a shipyard, but were not members of trades that regularly used asbestos. Rather, they were exposed to the dust created by other employees placing or removing insulation.

Evidence of ubiquitous general population exposure and environmental contamination from the spraying of asbestos on the steel-work of high rise buildings was established by 1972. Data by Nicholson and Pundsack (1973) showed that asbestos was commonly found at concentrations of nanograms per cubic meter (ng/m^3) in virtually all United States cities, and at concentrations of micrograms per liter (µg/l) in river systems of the United States. Concentrations of hundreds of nanograms per cubic meter were documented at distances up to one-quarter of a mile from fireproofing sites. Mesothelioma was acknowledged by the Advisory Committee to be associated with environmental exposures, but they suggested that "the evidence relates to conditions many years ago .... There is no evidence of a risk to the general public at present." Further, their report stated that, "There is at present no evidence of lung damage by asbestos to the general public," and "Such evidence as there is does not indicate any risk" from asbestos fibers in water, beverages, food, or

parenteral drugs. No mention was made in the report of risks from indirect occupational asbestos exposures.

2.1.3 Analytical Methodology

During the late 1960s and early 1970s, significantly improved methods were developed for assessing asbestos disease and quantifying asbestos in the environment. In 1971, a standardized methodology was established for the identification of pneumoconiosis: the ILO U/C Classification of Pneumoconioses (International Labour Office, 1971). This methodology provided a uniform criterion for assessing the prevalence of asbestos-related X-ray abnormalities.

Significant advances were also achieved in the quantification of asbestos aerosols. In the late 1960s, the membrane filter technique was developed for the measurement of asbestos fibers in workplace aerosols. While this procedure has some limitations, it did establish a standardized method, using simple instrumentation, that was far superior to any that existed previously. This method subsequently allowed epidemiological studies to be done that based exposure estimates on a standardized criterion. Experimental techniques in the quantification of asbestos at concentrations of tenths of ng/m^3 of air and tenths of µg/l of water were also developed, extending the sensitivity of exposure estimates approximately three orders of magnitude below those of occupational aerosols and allowing assessment of general population exposures. Finally, techniques for the analysis of asbestos in lung and other body tissues were developed. Digestion techniques and the use of electron microscopy to analyze fibers contained in the digest and in thin sections of lung tissue showed that asbestos fibers were commonly present in the lung tissue of general population residents as well as individuals exposed in occupational circumstances.

2.1.4 Experimental Studies

Experimental animal studies using asbestos fibers confirmed the risks of lung cancer and mesothelioma from amosite, crocidolite, and chrysotile. In each case, the establishment of a risk in animals followed the association of the malignancy with human exposure. For example, a causal relationship between lung cancer and asbestos exposure in humans was suggested in 1935 and confirmed in the late 1940's, but was not described in the open literature in animals until 1967 (Gross et al., 1967). Mesothelioma, reported in an asbestos

worker in 1953 (Weiss, 1953), was produced in animal experimentation in 1965 (Smith et al., 1965). Other animal experimentation showed that combinations of asbestos and other carcinogenic materials produced an enhanced risk of asbestos cancer. Asbestos exposure combined with exposure to benz(a)pyrene was demonstrably more carcinogenic than exposure to either agent alone. Additionally, organic and metal compounds associated with asbestos fibers were ruled out as important factors in the carcinogenicity of fibers. Lastly, animal experimentation involving the application of fibers onto the pleura of animals indicated that the important factor in the carcinogenicity was the length and width of the fibers rather than their chemical properties (Stanton, 1973). The greatest carcinogenicity was related to fibers that were less than 2.5 μm in diameter and longer than 10 μm.

2.2 CURRENT ASBESTOS STANDARDS

The current Occupational Safety and Health Administration (OSHA) standards for an 8-hour time-weighted average (TWA) occupational exposure to asbestos is 2 fibers longer than 5 μm in length per milliliter of air (2 f/ml or 2,000,000 f/m^3). Peak exposures of up to 10 f/ml are permitted for no more than 10 min (Code of Federal Regulations, 1984a). This standard has been in effect since July 1, 1976, when it replaced an earlier one of 5 f/ml (TWA). In Great Britain, a value of 0.5 f/ml is now the accepted level for chrysotile. This standard has evolved from recommendations made in 1979 by the Advisory Committee on Asbestos (1979a), which also recommended a TWA of 0.5 f/ml for amosite and 0.2 f/ml for crocidolite. From 1969 to 1983, 2 f/ml (TWA) was the standard for chrysotile (British Occupational Hygiene Society, 1968). This earlier British standard served as a guide for the OSHA standard (National Institute for Occupational Safety and Health, 1972).

The 1969 British standard was developed specifically to prevent asbestosis among working populations; data that would allow a determination of a standard for cancer (British Occupational Hygiene Society, 1968) were felt to be lacking. Unfortunately, among occupational groups, cancer is the primary cause of excess death among workers (see Chapter 3). Three-fourths or more of asbestos-related deaths are from malignancy. This fact led OSHA to propose a lowered TWA standard to 0.5 f/ml (500,000 f/m^3) in October, 1975 (Federal Register, 1975). The National Institute for Occupational Safety and Health anticipated

hearings on a new standard and proposed a value of 0.1 f/ml (National Institute for Occupational Safety and Health, 1976) in an update of their 1972 criteria document. In the discussion of the NIOSH proposal, it was stated that the value was selected on the basis of the practical limitations of analytical techniques using optical microscopy, and that 0.1 f/ml may not necessarily protect against cancer. The preamble to the OSHA proposal acknowledges that no information exists by which to define a threshold for asbestos carcinogenesis. The OSHA proposal has been withdrawn, and a new proposal was submitted on April 10, 1984 (Federal Register, 1984a). In it, OSHA proposed a TWA standard of either 0.2 or 0.5 f/ml, depending upon information to be obtained in hearings (held during the summer of 1984). NIOSH reaffirmed its position on a 0.1 f/ml TWA standard (Occupational Safety and Health Administration, 1984).

The existing Federal national emission standards for asbestos are published in Part 61, Title 40, Code of Federal Regulations (1984b). In summary, these apply to milling, manufacturing, and fabrication sources, and to demolition, renovation, and waste disposal, and include other limitations. In general, the standards allow compliance alternatives, either (1) no visible emissions, or (2) employment of specified control techniques. The standards do not include any mass or fiber count emission limitations. However, some local governmental agencies have numerical standards (e.g., New York: 27 ng/m^3), but these have little regulatory relevance.

3. HUMAN HEALTH EFFECTS ASSOCIATED WITH OCCUPATIONAL EXPOSURE TO ASBESTOS

3.1 INTRODUCTION

The evidence that asbestos is a human carcinogen is overwhelming. Studies on more than 30 cohorts of workers exposed to asbestos have demonstrated an elevated risk of cancer at the 5% level of significance. All four major commercial varieties have been linked to excess cancer and asbestosis. The question is not so much what disease, but how much disease. Our concerns are now more quantitative than qualitative. What are the dose, time, and age relationships for the different asbestos cancers? Are there differences in the carcinogenic potencies of the different asbestos minerals? What are the cancer risks at low exposures? What are the estimates of uncertainty?

This chapter is largely concerned with those studies that provide quantitative exposure-response relationships for asbestos diseases. While lung cancer and mesothelioma are the most dominant asbestos-related malignancies, the strength of the evidence and the relative excess of cancers at other sites are discussed. Models for assessment of the risk of lung cancer and mesothelioma are reviewed. Unit exposure risks are estimated from 14 studies that provide information on exposure-response relationships. These estimates illustrate considerable variation in the calculated unit exposure risks for mesothelioma and lung cancer in the different studies. The magnitude and possible sources of these different unit risks are discussed. The extent to which the variation is the result of methodological or statistical uncertainties (i.e., on the estimates of exposure or of the magnitude of disease) or of differences in the character of the exposure in terms of fiber size and mineralogical species is considered in detail.

3.2 MORTALITY ASSOCIATED WITH ASBESTOS EXPOSURE

The study of U.S. and Canadian insulation workers by Selikoff et al. (1979) contains the largest number of asbestos-related deaths among any group of asbestos workers studied. Thus, it best demonstrates the full spectrum of disease from asbestos exposure. The mortality experience of 17,800 asbestos insulation workers was studied prospectively from January 1, 1967 through

December 31, 1976. These workers were exposed primarily to chrysotile prior to 1940, to chrysotile and amosite from 1940 through 1965, and largely to chrysotile thereafter. No crocidolite is known to have been used in the U. S. insulation material (Selikoff et al. 1970). The workers mainly applied new insulation; removal of old materials would have constituted less than 5% of their activities.

In this group, 2271 deaths occurred, and their analysis provides important insights into the nature of asbestos disease. Table 3-1 lists the expected and observed deaths by cause, and includes data on tumors less frequently found. Lung tumors were common and accounted for approximately 21 percent of the deaths; 8 percent were from mesothelioma of the pleura or peritoneum, and 7 percent died from asbestosis. Considering all cancers, 675 excess malignancies occurred, constituting 30 percent of all deaths. In addition to lung cancer and mesothelioma, the incidences of cancers of the gastrointestinal tract, larynx, pharynx and buccal cavity, and kidney were significantly elevated.

Other tumors were also increased, but not to a statistically significant degree for individual sites. However, these other cancers, as a group, were significantly in excess: 184 observed (using best available evidence for classification) versus 131.8 expected ($p<0.001$). Some of this excess, however, may be the result of misclassification of asbestos-related lung cancer or peritoneal mesothelioma. Rather than 184 deaths, certificate of death classification attributed 252 cancers to these other sites. After a review of pathological material and available medical records, pancreatic, liver, and unspecified abdominal cancers are found to be commonly misclassified. Individuals certified as dying of cancers of the pancreas and the abdomen were often found to have peritoneal mesotheliomas, and several liver cancers were the result of a primary malignancy in the lung. As it was not possible to review all cases, some additional misclassification may still exist. However, its magnitude would not be great compared to the remaining excess of 52 cases. The excess at extra-thoracic sites may reflect mortality from the dissemination of asbestos fibers to various organs (Langer, 1974). Alternatively, it has been suggested that asbestos could exert a systemic effect, perhaps on the immune system, that leads to a general increased risk of cancer (Goldsmith, 1982).

TABLE 3-1. DEATHS AMONG 17,800 ASBESTOS INSULATION WORKERS IN THE UNITED STATES AND CANADA, JANUARY 1, 1967 - DECEMBER 31, 1976, NUMBER OF MEN 17,800, MAN-YEARS OF OBSERVATION 166,853

Underlying cause of death	Number of Deaths			Ratio of observed to expected	
	Expected[a]	Observed BE	Observed DC	BE	DC
Total deaths, all causes	1658.9	2271	2271	1.37	1.37
Total cancer, all sites	319.7	995	922	3.11	2.88
Cancer of lung	105.6	486	429	4.60	4.06
Pleural mesothelioma	-[b]	63	25	-[b]	-[b]
Peritoneal mesothelioma	-[b]	112	24	-[b]	-[b]
Mesothelioma, n.o.s.	-[b]	0	55	-[b]	-[b]
Cancer of esophagus	7.1	18	18	2.53	2.53
Cancer of stomach	14.2	22	18	1.54	1.26
Cancer of colon-rectum	38.1	59	58	1.55	1.52
Cancer of larynx	4.7	11	9	2.34	1.91
Cancer of pharynx, buccal cavity	10.1	21	16	2.08	1.59
Cancer of kidney	8.1	19	18	2.36	2.23
Cancer of pancreas	17.5	23	49	1.32	2.81
Cancer of liver and biliary passages	7.2	5	19	0.70	2.65
Cancer of brain	10.4	14	17	1.35	1.63
Cancer of lymphatic and hematopoietic system	33.2	34	31	1.02	0.93
All other cancer	63.5	108	136	1.65	2.16
Noninfectious pulmonary diseases, total	59.0	212	188	3.59	3.19
Asbestosis	-[b]	168	78	-[b]	-[b]
All other causes	1280.2	1064	1161	0.83	0.91

BE = Best evidence. Number of deaths categorized after review of best available information (autopsy, surgical, clinical).

DC = Number of deaths as recorded from death certificate information only.

[a]Expected deaths are based upon white male age-specific U.S. death rates of the U.S. National Center for Health Statistics, 1967-1976. (National Center for Health Statistics, 1977).

[b]Rates and thus ratios are not available, but these have been rare causes of death in the general population.

Source: Selikoff et al. (1979).

3.2.1 Accuracy of Cause of Death Ascertainment

Table 3-1 lists the observed deaths according to the cause recorded on the certificate of death (DC) and according to the best evidence (BE) available from medical records, surgical specimens, and autopsy protocols. In comparing occupational mortality with that of the general population, one usually utilizes information as recorded on death certificates since such information, without verification, serves as the basis for "expected rates." However, since mesothelioma and asbestosis are virtually unseen in the general population, their misdiagnosis (which has been common) is of little importance. In contrast, their misdiagnosis among asbestos workers can cause serious distortions in cause-specific mortality. Not only are asbestos-related causes understated, but others, such as pancreatic cancer, might wrongly appear to be significantly elevated (Selikoff and Seidman, 1981). While substantial differences exist in the DC and BE characterization of deaths from mesothelioma, asbestosis, pancreatic cancer, and liver cancer, the numbers of BE and DC deaths from cancer of other specific sites agree reasonably well.

Mesothelioma is best described by an absolute risk model and lung cancer by a relative risk model. Thus, risks for mesothelioma are expressed in absolute rates (e.g., deaths/1000 person-years), and the best medical evidence is used, when available, to establish the number of cases. Deaths from asbestosis are treated similarly. Risks for lung cancer are quantified by the ratio of observed to expected deaths. Here, it is expected that misclassification of lung cancer deaths would occur as frequently in asbestos workers as in the general population (in terms of the percentage of lung cancer cases). Therefore, the certificate of death cause is used to establish the relative risks of lung cancer in asbestos-exposed groups. However, when possible, account is taken of deaths from mesothelioma and asbestosis. The treatment of other malignancies also uses DC causes of death.

3.3 EPIDEMIOLOGICAL STUDIES OF ASBESTOS HEALTH EFFECTS: STRENGTH OF THE EVIDENCE

Many epidemiological studies have documented the presence of asbestos disease among occupationally-exposed workers. The larger and more recent studies are listed in Table 3-2 according to the type of fiber exposure and

TABLE 3-2. OBSERVED AND EXPECTED DEATHS FROM ALL CAUSES, LUNG CANCER, GASTROINTESTINAL CANCER, AND MESOTHELIOMA IN 41 ASBESTOS-EXPOSED COHORTS

	Industry	Country	Sex	COHORT Total Number	COHORT % Untraced	Years of follow-up	Years from onset	ALL DEATHS Obs.	ALL DEATHS Exp.	ALL DEATHS SMR	LUNG CANCER[a] Obs.	LUNG CANCER[a] Exp.	LUNG CANCER[a] SMR	GI CANCER[a] Obs.	GI CANCER[a] Exp.	GI CANCER[a] SMR	Number of mesotheliomas PI	Number of mesotheliomas Per	Unspec	Asbestosis	Other cancers in excess at 95% sign. level
Chrysotile																					
Acheson et al. (1982)[d]	Gas mask	UK	F	570	0.9	1951-1980	10+	177	148.5	119	6	4.5	133	4	4.9	82	1	0			
Dement et al. (1983)[d]	Textiles	USA	M	1291	2.1	1940-75	15+	245	152.5	161	33	9.8	336*	10	8.1	124	0	1			
McDonald et al. (1983a,b)[b]	Textiles	USA	M	2543		1938-77	20+	570	447.	127	59	29.6	200*	24	17.1	152*	0	1		17	
McDonald et al. (1980)	Mining	Canada	M	9767	10.0	1926-75	20+	3491	3010.3	109	230	184.6	125*	209	203.7	103	10	0		46	
McDonald et al. (1980)	Mining	Canada	F	440	7.0	1926-75	20+	84			2	1.2	83	0			1	0		0	
Nicholson et al. (1979)[c]	Mining	Canada	M	544	6.0	1961-77	20+	178	159.9	111	25	11.1	225*	10	9.5	105	1			26	
McDonald et al. (1984)	Frict. prod.	USA	M	3177	3.5	1938-77	20+	803	740.1	109	73	49.1	149*	39	51.6	114	6[e]	0		0[e]	
Rubino et al. (1979)	Mining	Italy	M	952	2.0	1946-75	20+	229	160.2	137	9	8.7	103	15	16.5	103	1[e]	0		21.1	Larynx[e]
Weiss (1977)	Manufacturing	USA	M	254	6.1	1941-74		56	108.8	61	4	4.3	93	4	3.8	105	0	0			
Predominantly chrysotile (>90%)																					
McDonald et al. (1983a)[b]	Tex. frict.	USA	M	4137	2.7	1938-77	20+	895	821.1	109	53	50.5	105	54	47.9	113	10	4		59	
Robinson et al. (1979)[b]	Tex. frict.	USA	M	2722	2.1	1940-75	0	912	741.3	123	49	36.1	136*	50	41.4	121	4	5	4	59.5	
Robinson et al. (1979)[b]	Tex. frict.	USA	F	554	3.1	1940-75		128	88.3	145	10	1.7	824*	8	6.8	133	1	1	2	13.1	
Mancuso & [illegible]-stler (1967)[b]	Tex. frict.	USA	MF	1491		1940-64		330	139.7	236	33	14.0	223*	16	8.9	180*	1	0		11	
Peto (1977)[f]	Textiles	UK	M	822	3.2	1933-74	10+	293	224.9	130	49	22.9	214*	16	15.7	102	5	0		20.6	
Thomas et al. (1982)[f]	Cement prod.	UK	M	1552	3.3	1936-77	15+	251	243.2	107	22	25.0	85	14	16.1	95	2	0		0	
Amosite																					
Acheson et al. (1984)[b]	Manufacturing	UK	M	4828	0.5	1947-78		333	298.8	111	57	29.1	196*	19	17.1	111	4	1		8.9	
Seidman et al. (1979)	Manufacturing	USA	M	820	4.6	1961-76	5+	528	397.2	133	83	23.8	349*	28	22.7	123	7	7		34	
Predominantly crocidolite[i]																					
Acheson et al. (1982)	Gas mask	UK	F	757	2.6	1951-80	10+	213	201.5	107	13	6.6	197*	5	4.0	125	3	2			Ovary
Hobbs et al. (1980)	Mining	Austral.	M	6208	20.0	1938-78	15+	826	547.2	98	68	30.2	157*				17	0		14	
Jones et al. (1980)[b]	Gas mask	UK	F	951	39.2	1941-78		166			12	6.3	190*	10	20.3	49	11	4			
Wignall & Fox (1982)[b]	Gas mask	UK	F	523	0.5	1951-77	10+	133	139.6	96	10	3.7	273*	7	10.7	65	0	2		1	Ovary
McDonald & McDonald (1978)	Gas mask	Canada	MF	179	11.6	1939-75		63			7	2.4[a]	875*				1	6		4	
Anthophyllite																					
Neuman et al. (1974)	Mining	Finland	MF	1092	4.7	1936-69		248			21	12.6	167*	7	16.9	47	0	0		13	
Talc (Tremolite)																					
Kleinfeld et al. (1974)	Mining	USA	M	258		1944-69	15+	100			13	4.5	289*	7	6.9	101	0	1		29	
Brown et al. (1978)	Mining	USA	M	398	4.0	1947-75		74	61.3	120	9	3.3	270*	3	3.8	188	0	0	1[e]	3.7	
Mixed fibrosures																					
Albin et al. (1984)	Cement prod.	Sweden	M	536	3.8	1957-80	10+	172	157.4	109	12	6.6	181*	13	10.6	176*	4	0		10.1	
Berry & Newhouse (1983)	Frict. prod.	UK	M	7470		1942-80	10+	1319	1361.8	96	143	120.5	101	103	107.2	96	0	0			
Berry & Newhouse (1983)	Frict. prod.	UK	F	1708		1942-80	10+	299	328.0	91	6	11.3	53	29	27.4	106	2	0			
Elmes & Simpson (1977)	Insulation	UK	M	178	2.9	1940-75		122	55.5	220	27	5	540*	13	1	1300*	0	5	11[b]	19	
Finkelstein (1983)	Cement prod.	Canada	M	241	3.3	1963-80	15+	72	42.5	169	20	3.3	606*	4	2.5	160	0	1		1.5	
Henderson & Enterline (1979)	Manufacturing	USA	M	1078		1941-73	Rel.	781	648.7	120	63	23.3	270*	15	19.9	130*	5	0		56	
Selikoff et al. (1979)	Insulation	USA	M	17800		1967-76	20+	1946	1376.0	141	306	93.7	416*	85	53.2	157*	63	112-		150	Kidney
Selikoff et al. (1979)	Insulation	USA	M	632		1943-76	20+	469	319.9	147	93[e]	13.1	710*	42[e]	14.0	>291*	11	27		41	
Kleinfeld et al. (1967)	Insulation	USA	M	152		1945-65	15+	46			10	1.4[a]	703*	5	1.8	278*	1	2		2	
Kaldor et al. (1980)	Shipyard	USA	M	4379	0.0	1950-78	20+	112	116.5	96	12	7.5	177				0[e]	0			
Newhouse & Berry (1979)	Manufacturing	UK	M	6680		1936-75	10+	545	458.8	119	103	43.2	238*	46	34	138	13	27		16.3	
Newhouse & Berry (1978)	Manufacturing	UK	F	922	23.	1936-76	10+	200	118.6	169	27	3.2	843*	20	10.2	196*	10	0		6.7	
Nicholson (1976a)	Manufacturing	USA	MF	685	0.0	1959-71	20+	199	134.1	148	27	8.4	321*	13	5.8	224*	5	7		24	
Puntoni et al. (1979)	Shipyard	Italy	M	42647		1960-75		1878	851.7	125	123	54.9	224*	66	46.6	136				50.6	Kidney, urinary organs, and larynx
Rossiter & Coles (1980)	Shipyard	UK	M	6232	3.4	1947-78		1843	990.4	186	84	100.3	84	63	76.2	83			21	9	
Wolff (1984)	Cement prod.	USA	M	5645	25.	1940-74	20+	681	898.1	66	51	49.2	104	25	58.1	58	0[e]	0			

Footnotes for Table 3-2

a. The deaths from lung cancer and gastrointestinal cancer are those designated on the certificate of death. The cases of mesothelioma are those determined from the review of all available evidence. Such cases will not be included with the lung cancers. The asbestosis cases will be those specifically listed, when provided. Otherwise, the number will be the difference between the observed and expected for non-infectious respiratory disease. The latter can be identified by the use of the decimal point notation.

b. Two studies of the same plant but with different cohort definitions.

c. The majority of this cohort would also be included in that of McDonald et al. (1980).

d. No mesotheliomas were identified in the defined cohort. However, three mesotheliomas, two in women and one in an individual terminated prior to 1937, from this plant have been identified in the Tumor Registry of Connecticut (Teta et al., 1983).

e. Twelve cases of pneumoconiosis were identified in this cohort. However, these were all in individuals who had previous exposure to anthracite coal containing silica.

f. Death certificate diagnosis of mesothelioma based upon clinical findings and analysis of pleural fluid. No histological material was available for review.

g. Significant at the 5 percent level in the entire cohort.

h. Three studies of the same plant at different periods of time and with different cohort definitions. Between 3000 and 6000 tons of chrysotile were used annually. Amosite constituted less than 1 percent of the asbestos used except for a 3-year period, 1942-1944, where an average of 375 tons per year were used. Crocidolite usage was approximately 3-5 tons per year (Robinson et al., 1979).

i. Between 1931 and 1970 an average of 60 tons of crocidolite per year were used (Berry et al., 1979). This would probably constitute about 1 percent of the total fiber usage.

j. The factory operated between 1932 and 1980. Between 1932 and 1935 crocidolite and chrysotile asbestos were used; thereafter, only chrysotile. The two mesotheliomas in this study were in the group exposed to both chrysotile and crocidolite.

k. Amosite was the predominant fiber used. However, chrysotile was also used between 1946 and 1973.

l. All of the groups in this category had a high exposure to crocidolite. In some cases, however, there was also a substantial exposure to chrysotile as well.

m. Two cohorts at the same facility with different definitions and follow-up periods.

n. Estimated as a proportion of deaths.

o. May have had exposure to asbestos in the construction industry.

p. Pleural mesothelioma or lung cancer.

q. Number of deaths based upon a review of all medical evidence.

r. No cases observed through the period of follow-up. Three cases have occurred subsequently.

s. No cases occurred in the cohort as defined during the period of observation. Two occurred in individuals prior to 20 years from onset of employment and nine cases (8 pleural and 1 peritoneal) have developed subsequent to termination of follow-up (Weill, 1984).

*p <0.05.

work circumstance. Of the 41 groups listed, significantly increased (at the 5% level with a one-sided test) lung cancer is found in 32. Gastrointestinal cancers are elevated at a significant level in 10. Moreover, strong exposure-response relationships are seen for lung cancer and mesothelioma. They are also seen for gastrointestinal cancer, but to a lesser extent.

The follow-up period was relatively long in most of the studies listed in Table 3-2. However, in many cohorts, individuals continued to enter the studies through the follow-up years, particularly in the period after World War II. Thus, many individuals in some groups are just now reaching a time of high potential risk for mesothelioma (30 or more years from onset of exposure). In some cases, this can be seen in the finding of substantially increased risks of mesothelioma subsequent to the termination of follow-up (see Table 3-2 footnotes).

3.4 MATHEMATICAL MODELS OF HUMAN CARCINOGENESIS

The quantitative determination of cancer risk in an occupational group can be used to predict risks in similar exposure circumstances in the absence of any model of action; observations in one group would apply to identically exposed workers. If, however, a risk determination fits within the framework of a general mathematical model for cancer, then predictions outside the range of measurement can be made within the range of validity of a model. Validation of a mathematical model, of course, requires the testing of such predictions. If a mathematical model has a mechanistic basis, e.g., at a molecular level of action, its use is considerably strengthened. To the extent that a model is applicable, it strengthens risk estimates made for exposures and times different from those directly observed. To the extent that a model may be applicable, it points to issues that must be considered in any general risk assessment.

In the case of human carcinogenesis, a variety of multistage models have been proposed to describe a number of observations, most notably the power law dependence of human cancer risk with age and the time and dose dependence of induced malignancy in some animal experiments. The models were initially suggested to explain the observation that site-specific cancer mortality increases as the fifth or sixth power of age (e.g., Cook et al., 1969; Armitage and Doll, 1954). The models suggested ranged from proposals that multiple (up to six or seven) mutations (or carcinogenic events) occur in the

same or adjacent cells (Muller, 1951; Fisher and Holloman, 1951; Nordling, 1953) to models that involve preferential clonal development of altered cell lines (Fisher, 1958; Armitage and Doll, 1957, 1961). Depending on the model, some or all of the states are capable of being affected by an external carcinogen. For those susceptible states, it is expected that the probability of progression to the next stage would be proportional to the time that a carcinogenic agent, or its active metabolite, is at a reaction site. A constant exposure to environmental carcinogens would then introduce a power of time for each state that is affected by a particular external carcinogen. Powers of time also arise from exposure-independent processes. It is important to note, however, that a power of dose is introduced for each exposure-dependent step (for short-term exposures). Motivated by the experimental demonstration of initiation and promotion in skin cancer (Berenblum and Shubik, 1949), Armitage and Doll (1957) discuss a two-state model with an intermediate time-dependent growth phase that is compatible with the observed age dependence of cancer incidence.

In its generalized form, the model suggests that the time dependence of site-specific cancer incidence in the general population is

$$I(t) = C\lambda_1\lambda_2 \ldots \lambda_k(t-w)^{k-1} \qquad (3\text{-}1)$$

where the λ_i are the transition probabilities of each state, k is the number of stages and w is the growth time for a fully transformed cell to become clinically detectable. One, or several, of the λ_i can be influenced by the application of an external carcinogen. There would be a power of dose (or intensity of exposure) for each stage so affected. To account for this, the most general form of the multistage model can be written

$$I(t) = C(q_0 + \Sigma_i q_i d^i)(t-w)^{k-1} \qquad (3\text{-}2)$$

Within this model, one can consider carcinogenic action on specific stages at different times in the carcinogenic process.

Whittemore (1977a, 1977b) and Day and Brown (1980) have explored some of the time courses of cancer risk that are predicted by the model. The important aspects of these analyses are:

1. The effects of early stage carcinogens are most important early in life (the cells or cell lines that are started in the carcinogenic process are available for a long time for further alteration). In addition, their effect diminishes slowly after cessation of exposures relative to continuous exposure.

2. The effects of late-stage carcinogens are most important late in life when many altered cells are available to be acted upon. The effects of exposure to late-stage carcinogens diminish rapidly after cessation of exposure.

3. For each stage that an externally applied carcinogen acts, there is a power of intensity of exposure (or dose for short-term exposures).

Thus, the predicted time dependence of cancer risk can be highly varied depending on the stage affected, and sublinear, as well as linear, dose-response relationships can be incorporated within the model. Here, sublinear refers to a relationship that contains a power of dose greater than unity. A supralinear relationship is not contained within the framework of the model.

The multistage model has provided a basis for dose-incidence extrapolation procedures. These have been formulated by Guess, Crump, and others (Guess and Crump, 1976, 1978; Guess et al., 1977). The procedure makes no a priori assumptions on the dose-response relationship, but utilizes a maximum likelihood procedure to calculate the q_i values along with their 95 percent confidence limits. In practice, it is found that most experimental carcinogenesis data cannot rule out a linear dose term. Thus, the 95 percent confidence limit on the risk at low exposure is dominated by the uncertainty on the linear term (Guess et al., 1977).

It should be noted that the exposure in the multistage model is to the site of action of an alterable cell. Significant non-linearities can be introduced into an exposure-response relationship by non-linearities in the metabolism of a chemical to an active species or in the detoxification of an active chemical. Such non-linearities have been observed in the case of vinyl chloride (Gehring et al., 1978). A general discussion of activation non-linearities in dose-response relationships has been published by Hoel et al. (1983).

Human data supporting a multistage model are limited because of lack of information on the age, time, and dose dependence of cancer risk from exposure to external agents. Recent data from the study of smoking effects among British doctors (Doll and Peto, 1978) suggest that the dose-response relationship is quadratic and that cigarette smoke may act at two stages, one early and one late, in the carcinogenic process. This concept is supported by the partial reduction in lung cancer risk after smoking cessation (relative to continued smoking). On the other hand, U.S. smoking data suggest a linear dose-response relationship (Hammond, 1966; Kahn, 1966). In the case of radiation, the long lasting increased risk of solid tumors among residents of Hiroshima and Nagasaki (Beebe et al., 1978) suggests an early stage action for radiation. However, the age dependence of risk demonstrates a risk that is proportional to the risk in the absence of radiation exposure, suggesting a late-stage action. The dose-response relationship, however, does not suggest a supra-linear relationship, which would be the case if two stages were affected. In contrast to a somewhat equivocal application to human data, the model describes very well the time and dose dependence of skin tumors in benzo(a)pyrene painted mice (Lee and O'Neill, 1971; Peto et al., 1975).

In summary, the multistage model provides a useful conceptual framework for considering the age, time and dose dependence of site specific cancer incidence. However, it is so general that it can be made to fit virtually any animal or human carcinogenesis dose-response data. The requirements are more stringent for fitting time-to-tumor data. Here, however, few human data are available for validation. At this time, the model cannot predict a priori either the dose or time dependence of human cancer. Nevertheless, the concepts of the model are plausible and warrant consideration when the data on the age, time, and dose dependence of asbestos cancers are reviewed.

3.5 LINEARITY OF EXPOSURE-RESPONSE RELATIONSHIPS

Direct evidence for linearity of response with asbestos exposure is available from seven studies (two of the same plant) that compared lung cancer mortality to the cumulative total dust exposure in asbestos workplaces (Dement et al.,.1982; Henderson and Enterline, 1979; McDonald et al., 1980, 1983a, 1983b; Finkelstein, 1983; Seidman, 1984). Figure 3-1 plots the exposure-response data in these studies as the ratio of observed to expected lung

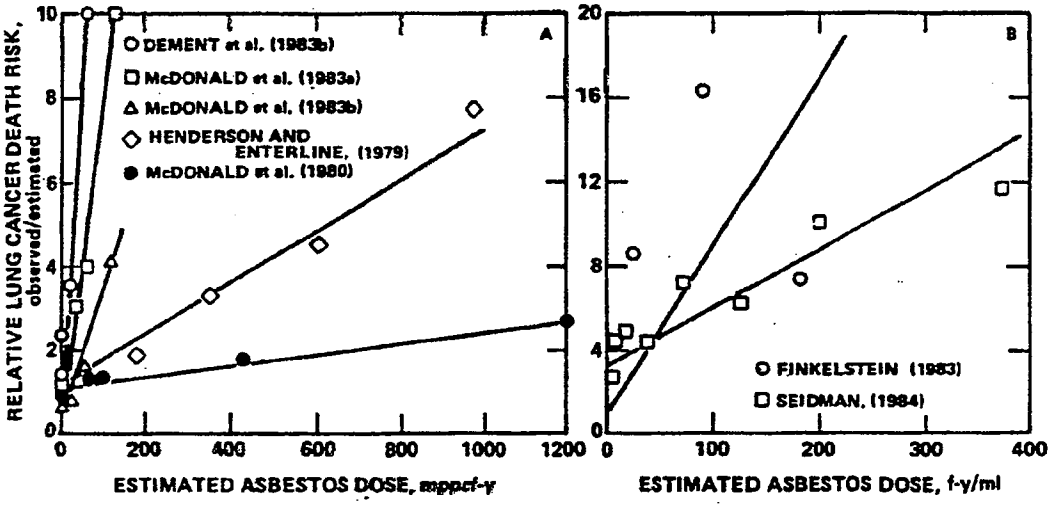

Figure 3-1. Exposure response relationships for lung cancer observed in seven studies. Cumulative exposures are measured in terms of millions of particles per cubic foot-years (mppcf-y) or fibers per milliliter-years (f-y/ml).

cancer mortality against the measured cumulative dust exposure in millions of particles per cubic foot-years (mppcf-y) or cumulative asbestos exposure in fiber-years per milliliter (f-y/ml). (Henceforth, the term "dose" will be used to designate cumulative exposure.) While different exposure-response relationships appear to exist for the five studies of Figure 3-1a, each demonstrates a very good linear relationship over the entire range of observation. The differences in the slopes of the relationships may relate to differences in the quantity of the other dust present, the fiber size distribution, the fiber type, the age of the population under observation, the representativeness of the dust sampling programs and possibly other factors. These factors are discussed later, when the exposure-response relationships of all available studies are compared (see Section 3.9). In the case of the two studies in Figure 3-1b, the form of the dose-response relationship is less clear, particularly for the group studied by Finkelstein (1983). The data from three other studies that provide dose-response information are not shown. In one (Weill et al., 1979), the dose-response relationship was affected by the large number of untraced individuals in the study; in two others of friction products manufacturing (Berry and Newhouse, 1983; McDonald et al., 1984), the relationship was too weak to provide any guidance as to its form. (These three studies are considered later, in Section 3.9.) In one case, when exposure-response relationships were analyzed according to both duration and intensity of exposure (McDonald et al., 1980), the results were less dramatic than shown in Figure 3-1a. However, this may be the result of small numbers; only 46 excess lung cancer deaths are reported in all exposure categories.

In the discussion of the time relationship of lung cancer risk and asbestos exposure, the data can be interpreted in terms of a multistage model of cancer in which asbestos appears to act at a single late stage. The continued high risk following cessation of exposure results from the continued presence of asbestos in the lungs. This model is compatible with a linear dose-response relationship and with the synergistic interaction between asbestos and cigarette smoking.

Fewer data are available on the exposure-response relationship for mesothelioma. Table 3-3 lists the mesothelioma mortality from four studies (Seidman, 1984; Hobbs et al., 1980; Jones et al., 1980; Finkelstein, 1983) in terms of cases per 1000 person-years of observation or percentage of mesothelioma deaths. The data of Seidman are presented both in terms of duration of employment and estimated cumulative fiber exposure. The exposure circumstances of

TABLE 3-3. THE RISK OF DEATH FROM MESOTHELIOMA ACCORDING TO THE TIME OF ASBESTOS EXPOSURE, IN FOUR STUDIES

Study	Exposure period (months unless noted)	Number of deaths	Estimated person-years (10+ years from first exposure)	Deaths/ 1000 person-years	Number exposed	Percent of deaths
Hobbs et al. (1980)						
	<3	0	21,213	0		
	3 - 11	10	19,548	0.5		
	12+	16	14,833	1.1		
Jones et al. (1980)						
	<5	0			314	0
	5 - 10	3			116	2.6
	10 - 20	4			145	2.8
	20 - 30	4			101	4.0
	30+	5			51	9.8
Seidman (1984)						
	2.2	1	3,700	2.7		
	7.1	5	1,203	4.2		
	15.4	4	1,263	3.2		
	57	7	1,248	5.6		
	8.8[a]	2	4,104	0.5		
	37.5[a]	5	1,162	4.3		
	75[a]	6	1,053	5.7		
	125[a]	2	420	4.8		
	200[a]	1	425	2.4		
	375[a]	1	250	4.0		
Finkelstein (1983)						
	44	1		1.9		
	92	2		4.9		
	180	6		11.9		

[a]Exposure in fiber-years/ml.

the groups studied by Jones et al. (1980) and Seidman (1984) offer the ideal circumstances for studying the effects of cumulative exposure on risk. The average exposure duration of each group was short (less then two years) and all individuals began exposure at approximately the same time during World War II. Thus, the confounding effect of time on the observed risk 20 or more years from onset of exposure is largely removed. To the extent that the distributions in duration and time from onset of employment are similar in the different exposure categories of Finkelstein (1983) and Hobbs et al. (1980), the data would reflect an exposure-response relationship. This is likely to be approximately correct, but direct information is not available.

Figure 3-2 displays the data of Table 3-3. To the extent that duration of employment is related to dose, the studies of Jones et al. (1980) and Hobbs et al. (1980) are compatible with a linear dose-response relationship, as is that of Finkelstein (1983). The study of Seidman (1984) is highly non-linear, especially when mesothelioma risk is plotted against estimated dose in f-y/ml. The relationship, however, is supralinear (i.e., one involving fractional powers of dose). This is likely to be the result of statistical uncertainties associated with small numbers rather than exposure misclassification; in the case of lung cancer a highly linear dose-response relationship was observed, albeit one that suggested a zero dose intercept at an SMR (standard mortality ratio) greater than 100.

Polynomials of degree one and two were fitted to the data of Jones et al. (1980), Hobbs et al. (1980), and Finkelstein (1983). The effect of including a quadratic term is shown in Table 3-4. In no case is a quadratic term required; in one case its coefficient is negative, indicating a supralinear relationship, and in the case where the effect is greatest (Finkelstein, 1983), the effect on the slope at zero dose is only a factor of 1.76. A quadratic term for the data of Seidman (1984) is clearly unwarranted.

A final study which provides some dose-response information is that of Newhouse and Berry (1979), which shows an increasing risk of mesothelioma with increasing duration and intensity of exposure (Table 3-5). However, a quantitative relationship cannot be determined.

Because of the limited dose-response data, the model for mesothelioma is not as well established as that for lung cancer. As will be seen, the time course of mesothelioma appears to be related only to the asbestos exposure. At this time, no interactive effects have been observed between asbestos and

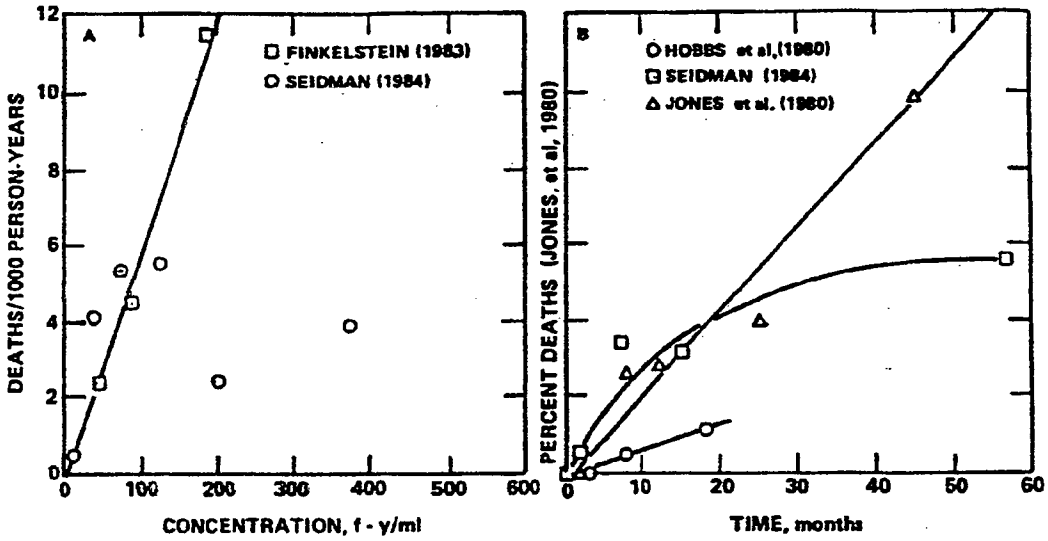

Figure 3-2. Exposure-response relationships for mesothelioma observed in four studies. Exposures are measured in terms of fiber per milliliter-years (f-y/ml) or duration of employment.

TABLE 3-4. ANALYSIS OF RESIDUALS IN POLYNOMIAL FIT TO OBSERVED MESOTHELIOMA DOSE-RESPONSE DATA

Study	Sum of Squares Accounted for by: Linear term	Quadratic term	Residual	Probability[a]	Ratio of slopes[b]
Hobbs et al., 1980	0.8133	0.0015	0.0067	0.72	0.85[c]
Jones et al., 1980	77.64	0.51	2.92	0.39	1.38
Finkelstein, 1983	78.50	1.19	0.27	0.28	1.76

[a]The probability that the observed deviation from linearity is by chance alone.

[b]The ratio of the slope of the dose-response function at zero dose without and with inclusion of a quadratic term.

[c]The sign of the quadratic term is negative indicating a supralinear relationship (i.e., one containing fractional powers of dose).

TABLE 3-5. RISK OF MESOTHELIOMA/100,000 PERSON-YEARS WITH INCREASING DURATION AND INTENSITY OF EXPOSURE (Newhouse and Berry, 1979)

	Duration of exposure	Deaths/100,000 Person-Years Intensity of Exposure: Low-moderate[a]	Severe[b]
Males	<2 yrs	33	104
	>2 yrs	93	243
Females	<2 yrs	{48}	136
	>2 yrs	combined	360

[a]5-10 f/ml.

[b]>20 f/ml.

other agents in the etiology of the disease. The steep power law dependence of risk on time from asbestos exposure suggests that mesothelioma can be described within the framework of the multistage model (see Peto et al., 1982) and that asbestos may act early in the carcinogenic process. However, because asbestos has been shown to act late in the carcinogenic process in the case of lung cancer, it could do so also in the case of mesothelioma. If so, the dose-response relationship would involve higher than linear powers of dose.

While a quadratic component in the dose-response relationship has plausibility, the existing data provide no support for it. Further, the finding of mesothelioma among family contacts of workers suggests that a substantial risk exists at much less than occupational exposures among family contacts of chrysotile miners and millers and amosite factory workers. Among the miners and millers, 3 family member contact cases are known (McDonald and McDonald, 1980) compared to 12 among the miners and millers. For the amosite factory workers, there are 4 cases of family member contact mesothelioma compared to 15 cases due to occupational exposure (Anderson et al., 1976).

Even more limited data are available on a dose-response relationship for gastrointestinal (GI) cancer. As seen in Table 3-2, the strength of the evidence relating asbestos exposure to GI malignancy is less than that from lung cancer and mesothelioma; the excess relative risk, when present, is lower than that for lung cancer. Of the seven studies providing a clear dose-response relationship for lung cancer, information is available from six of them on a dose-response relationship for GI cancer. Weighted least squares regression analyses were run on the data of the studies. Table 3-6 lists the coefficients of these analyses, along with the standard errors of the slopes. As can be seen, five of the six studies which demonstrated a fairly steep dose-response relationship for lung cancer demonstrate a consistent and positive trend with exposure for GI cancer, but less strong than that for lung cancer. However, while indicating a positive trend with exposure, the data on GI cancer dose-response relationships are inadequate to establish the functional relationship between dose and risk.

This document uses a linear exposure-response relationship for estimating unit exposure risks for lung cancer and mesothelioma and for calculating risks at cumulative exposures 1/10 to 1/100 of those of the occupational circumstances of past years. It is a plausible relationship, and for lung cancer is strongly indicated by the existing evidence. While more limited data exist for mesothelioma, they also indicate a linear relationship. Its use has three distinct advantages: 1) point estimates of exposure-response can be made without knowledge of individual exposures, i.e., the excess mortality of an entire group can be related to the average exposure of the group; 2) extrapolation to various exposure circumstances can be made easily; and 3) it is likely to be a conservative extrapolation procedure from the point of view of human health. It is emphasized that linearity of exposure-response obtains only for similar times of exposure and observation among similarly aged individuals with similar personal habits.

TABLE 3-6. COMPARISON OF LINEAR WEIGHTED REGRESSION EQUATIONS FOR LUNG CANCER AND GI CANCER IN SIX COHORTS OF ASBESTOS-EXPOSED WORKERS

Study	Regression Equation[a]	
	Lung cancer	GI cancer
	Textiles	
Dement et al., 1983b	SMR = 151 + 4.19(±0.84)f-y/ml[b]	SMR = 34 + 1.18(±0.62)f-y/ml
McDonald et al., 1983a	SMR = 110 + 2.07(±0.25)f-y/ml %RR = 61 + 2.27(±0.63)f-y/ml[c]	SMR = 113 + 0.59(±0.37)f-y/ml %RR = 82 + 1.19(±0.42)f-y/ml
McDonald et al., 1983b	SMR = 53 + 0.86(±0.15)f-y/ml %RR = 70 + 1.20(±0.33)f-y/ml	SMR = 82 + 0.42(±0.19)f-y/ml %RR = 84 + 0.38(±0.32)f-y/ml
	Mining	
McDonald et al., 1980	SMR = 92 + 0.043(±0.008)f-y/ml	SMR = 88 + 0.011(±0.010)f-y/ml
	Manufacturing	
Seidman, 1984	SMR = 325 + 2.72(±0.54)f-y/ml	SMR = 110 + 0.084(±0.43)f-y/ml
Finkelstein, 1983	%RR = 100 + 4.79(±2.70)f-y/ml	%RR = 100 + 3.11(±0.16)f-y/ml

[a]Equations are calculated for the increased risk per f-y/ml of exposure. Data of McDonald et al., given in mppcf-y, were converted to f-y/ml using the relationship: 1 mppcf = 3 f/ml.

[b]± standard error of the coefficient of f-y/ml.

[c]%RR is relative risk x 100.

3.6 TIME AND AGE DEPENDENCE OF LUNG CANCER

A relative risk model has long been assumed to be applicable for the description of the incidence of lung cancer induced by occupational asbestos exposure. Such a model is tacitly assumed in the description of mortality in terms of observed and expected deaths. Virtually every study of asbestos workers is described in these terms. Early suggestive evidence supporting it is found in the synergistic action between asbestos exposure and cigarette smoking (Selikoff et al., 1968), in which the lung cancer risk from asbestos exposure depended on the underlying risk in the absence of exposure. Relative risk models were discussed previously by Enterline (1976) and Peto (1977) and utilized in projections of lung cancer from past asbestos exposure by Nicholson et al. (1982). They were adopted in the risk analyses of the Advisory Committee on Asbestos (1979a,b), the U.S. Consumer Product Safety Commission (1983), and the National Academy of Sciences (1984). Information on lung cancer risk from exposures at different ages is now available from two studies (Selikoff et al., 1979; Seidman, 1984). The analyses of these data, along with the observations of linear dose-response relationships, provide substantial support for the use of such a formulation for lung cancer.

Information from the insulation workers study by Selikoff et al. (1979) on the time course of asbestos cancer risk is given in Figure 3-3, which shows the relative risk (here taken to be the ratio of observed to expected deaths) of death from lung cancer according to age for individuals first employed between ages 15 and 24 and for those employed between ages 25 and 34. The two curves rise with the same slope and are separated by the 10 years of difference in age at first exposure. This suggests that the relative risk of developing asbestos-related lung cancer according to time from onset of exposure is independent of age and of the pre-existing risk at the time of exposure. In contrast, both the slope and the value of the excess risk of lung cancer are two to four times greater for the group first exposed at older ages compared to those exposed at younger ages. The similarity of the data for each group in Figure 3-3 suggests that the data be combined and plotted according to time from onset of exposure. The result, shown in Figure 3-4, plots the data according to years from onset of exposure. However, because of the great stability of union insulation work, the curve also reflects effects according to duration of exposure up to at least 25 years from onset of exposure. A linear increase with time from onset of exposure occurs for about 35 years

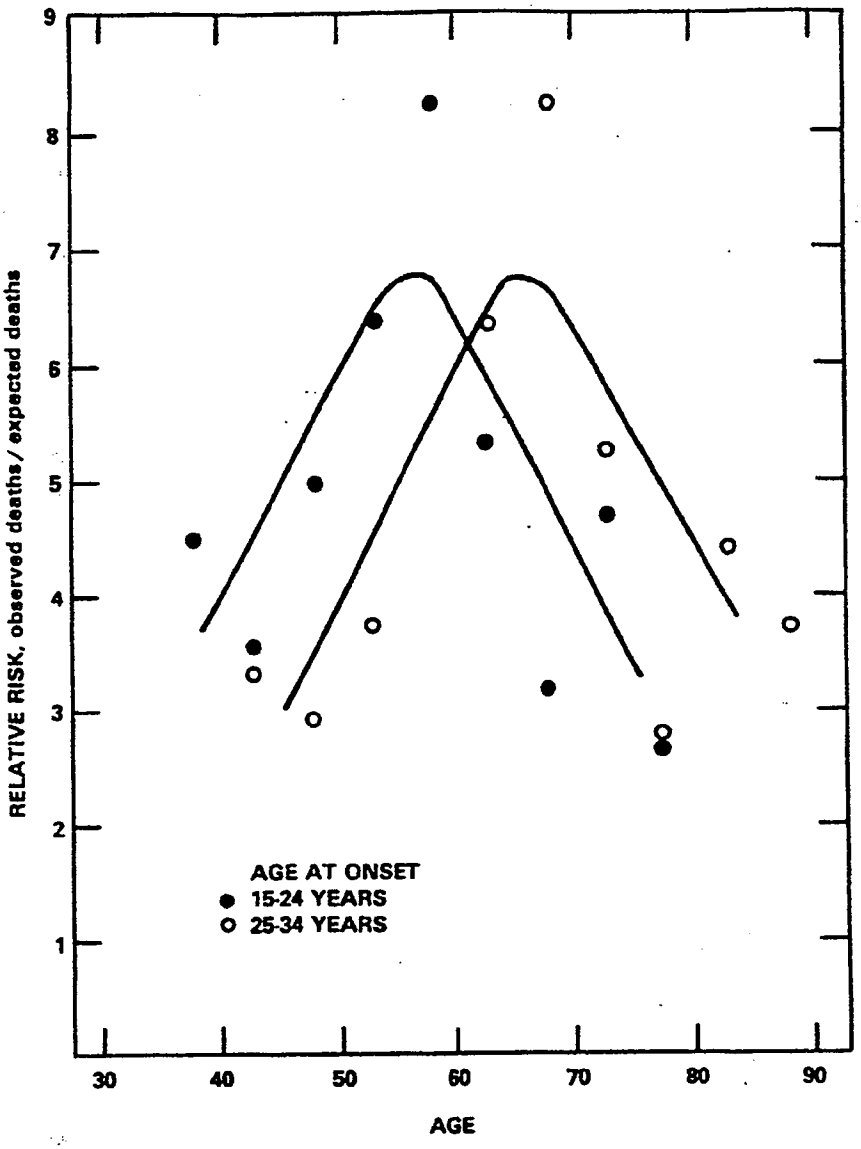

Figure 3-3. The relative risk of death from lung cancer among insulation workers according to age. Data supplied by I.J. Selikoff and H. Seidman.

Source: Nicholson (1982).

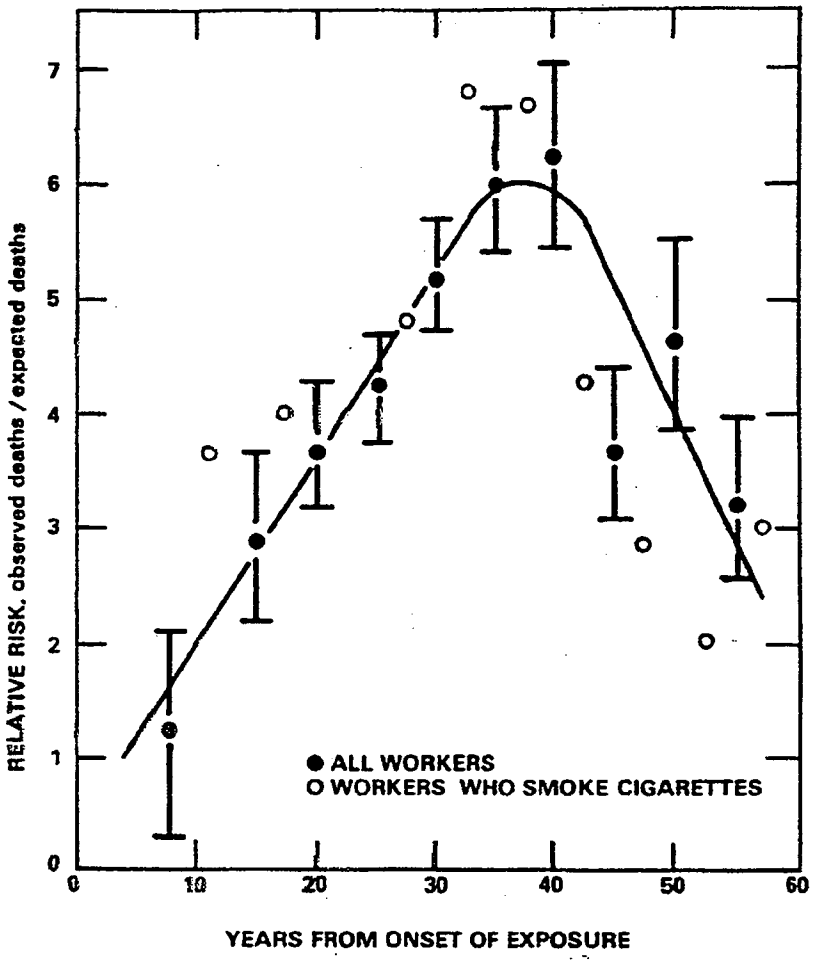

Figure 3-4. The relative risk of death from lung cancer among insulation workers according to time from onset of exposure (● all insulators; O indicates insulators who were smoking cigarettes at the start of follow-up in 1967.) Data supplied by I.J. Selikoff and H. Seidman.
Source: Nicholson (1982).

(to about the time when many insulation workers would have terminated employment), after which the relative risk falls substantially. The decrease is, in part, the result of the earlier deaths of smokers from the group under study due to their higher mortality from lung cancer and cardiovascular disease. However, the decrease is not solely the result of the deaths of smokers since a similar rise and fall occurs among those individuals who were smokers at the start of the study compared to smokers in the general population. Part of the decrease may relate to the elimination of asbestos, particularly chrysotile, from the lung; selection processes, such as differing exposure patterns (e.g., the survivors may have avoided intense exposures); or differing individual biological susceptibilities. While the exact reason for the effect is not understood, it is a general phenomenon seen in other mortality studies of asbestos workers (Nicholson, et al., 1979; 1985).

The early portions of the curves of Figures 3-3 and 3-4 have three important features. After a short delay, they show a linear increase in the relative risk of asbestos lung cancer according to time from onset of exposure. Figure 3-4 shows that this increased relative risk is proportional to the time worked, and, thus, to the cumulative asbestos exposure. However, the linear rise can occur only if the increased relative risk that is created by a given cumulative exposure of asbestos continues to multiply the underlying risk for several decades thereafter. Finally, an extrapolated linear line through the observed data points crosses the line of relative risk equal to one (that expected in an unexposed population) at between five and ten years from onset of exposure. This means that the increased relative risk appropriate to a given exposure is achieved soon after the exposure takes place. However, if there is a low underlying risk at the time of the asbestos exposure (as for individuals aged 20-30), most of the cancers that will arise from any increased risk attributable to asbestos will not occur for many years or even decades until the underlying risk becomes substantially greater.

The data of Seidman (1984) also show that exposure to asbestos multiplies the pre-existing risk of lung cancer and that the multiplied risk becomes manifest in a relatively short time. Figure 3-5 depicts the time course of lung cancer mortality beginning five years after onset of exposure of a group exposed for short periods of time. The average duration of exposure was 1.46 years; 77 percent of the population was employed for less than 2 years. Thus,

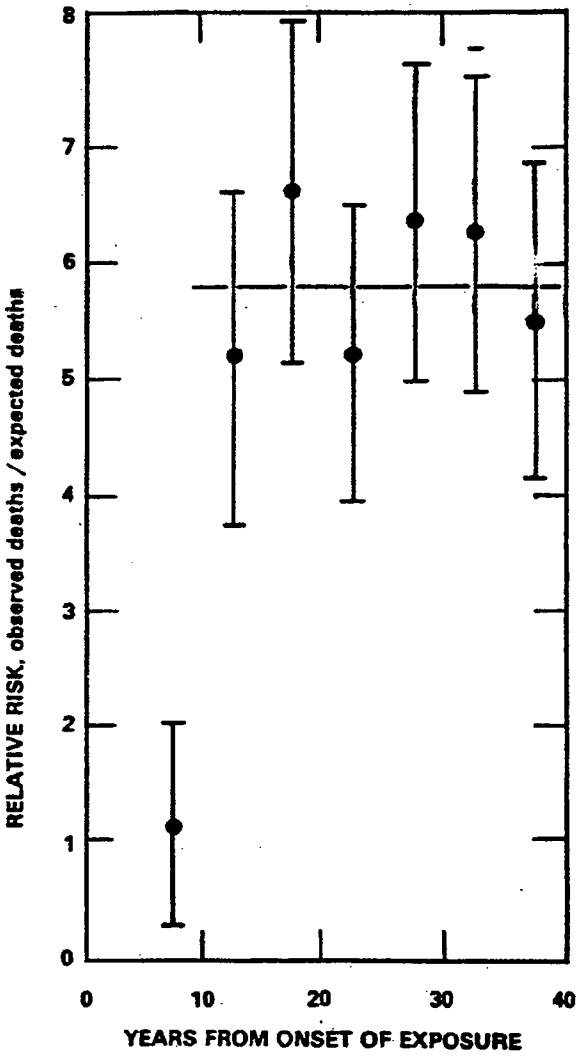

Figure 3-5. The relative risk of death from lung cancer (BE) among amosite factory workers according to time from onset of exposure.

Source: Seidman (1984).

exposure had largely ceased prior to the beginning of the follow-up period. A rise to a significantly elevated relative risk occurred within ten years and remained constant throughout the observation period of the study. Furthermore, the relative risk from a specific exposure is independent of the age at which exposure began, whereas the excess risk would have increased considerably with the age of exposure. Table 3-7 shows the relative risk of death from lung cancer for individuals exposed for less than and greater than 25 f-y/ml according to age at time of entrance into a ten-year observation period. Within a given age category, relative risk was similar during different decades from onset of exposure, as previously shown in Figure 3-5 with the overall data. However, relative risk also was independent of the age decade at entry into a ten-year observation period (see rows labeled "All" in each exposure category of Table 3-7). There is some reduction in the oldest, most heavily exposed group. This may be attributed to the same selection effects manifest at older ages in insulation workers.

In terms of carcinogenic mechanisms, it appears that asbestos acts largely like a lung cancer-promoting agent. However, because of the continued residence of the fibers in the lung, the promotional effect does not diminish with time after cessation of exposure as it may with chemical or tobacco promoters. Further, inhalation of the fibers can precede initiating events because many fibers remain continuously available in the lung to act after other necessary carcinogenic processes occur.

A feature of Figure 3-4 important in the assessment of asbestos carcinogenic risk is the decrease in relative risk after 40 years from onset of exposure, or 60 years of age. As mentioned previously, we do not have a full understanding of this decrease, but it generally applies. A virtually identical time course of lung cancer risk occurs in asbestos factory employees (Nicholson et al., 1985) and in Canadian chrysotile miners and millers (Nicholson et al., 1979). Because of the significant decrease at long times from onset of exposure and older ages, observations on retiree populations can seriously understate the actual risk of asbestos-related death during earlier years. To the extent that time periods between 25 and 40 years from onset of exposure are omitted from observation, a study will underestimate the full impact of asbestos exposure on death.

TABLE 3-7. RELATIVE RISK OF LUNG CANCER DURING 10-YEAR INTERVALS AT DIFFERENT TIMES FROM ONSET OF EXPOSURE

Years from onset of exposure	Age at start of period, years			
	40 - 49	50 - 59	60 - 69	70 - 79
	Less than 25 f-y/ml exposure			
5	0.0 [0.7][a]	1.4 (1)[b]	0.0 [4.1]	0.0 [0.7]
15	12.0 (3)	5.1 (4)	2.2 (3)	4.9 (5)
25	5.9 (1)	2.3 (2)	6.4 (9)	28.0 (3)
35	--	2.8 (1)	8.1 (6)	1.9 (1)
All	6.3 (4)	3.0 (8)	3.9 (18)	3.1 (9)
	Greater than 25 f-y/ml exposure			
5	0.0 [1.7]	12.9 (8)	6.6 (5)	3.7 (1)
15	7.7 (2)	11.1 (8)	5.6 (6)	6.2 (4)
25	25.0 (3)	9.7 (7)	12.0 (13)	2.1 (2)
35	--	4.3 (1)	4.0 (2)	8.8 (3)
All	8.3 (5)	10.5 (24)	7.6 (26)	4.5 (10)

[a] [] = no cases seen. Number of cases expected on the basis of the average relative risk in the overall exposure category.

[b] () = number of cases.

Source: Seidman (1984).

To appreciate the effect of the observed lung cancer time dependence upon the results of an epidemiological study, the excess risk of lung cancer was calculated for different observation periods for a hypothetical group exposed for 25 years beginning at age 20. The time course of the risk was set proportional to that of Figure 3-4 and 1978 general population rates were used. Table 3-8 lists the percent excess lung cancer mortality observed for three follow-up periods, 10 years, 20 years, and lifetime, beginning at different ages. As can be seen, the percent excess risk from start of exposure at age 20 to the complete death of all cohort members is 55 percent of the maximum. The percent excess risk increases up to age 50 as the follow-up period starts later, reflecting the increased relative risk concomitant with increased exposure. For observations starting after age 50 it falls substantially; follow-up begun at age 65 observes only 38 percent of the full risk. To the extent that a group under observation has an age distribution that is similar

TABLE 3-8. ESTIMATES OF THE PERCENTAGE OF THE MAXIMUM EXPRESSED EXCESS RISK OF DEATH FROM LUNG CANCER FOR A 25-YEAR EXPOSURE TO ASBESTOS BEGINNING AT AGE 20[a]

Age at start of observation, years	Period of follow-up, years			Years from onset of exposure
	10	20	Lifetime	
20	2	32	55	0
30	34	65	55	10
40	69	91	56	20
50	97	81	55	30
60	73	55	46	40
65	55	41	38	45
70	37	29	29	50

[a]The maximum expressed risk is that manifest 7.5 years after the conclusion of the 25-year exposure.

to the number alive in each quinquennium in a lifetime follow-up, an observation for any period of time would reflect the same mortality ratio as an observation from onset of exposure to the death of the total cohort.

The data in Table 3-8 came from observations on long-term exposures to high concentrations of asbestos (>10 f/ml) where preferential death of susceptible individuals occurred. Thus, appropriate comparisons between heavily exposed groups could be made on the basis of lifetime risk (i.e. 55 percent of the maximum), as well as on the maximum risk. However, in groups exposed to low levels (<0.1 f/ml), even for many years, selection effects may be much less important. A minimal excess risk would barely affect the pool of susceptible individuals. A lesser effect would also be expected from short-term exposures (to less than extreme concentrations). If selection effects are largely the cause of the disease, the maximum expressed relative risk would be most appropriate for estimating risks associated with low-level exposures. However, if the decrease is largely the result of elimination of asbestos from the lung or the biological neutralization of deposited fibers, a decrease in relative risk beginning at about 35 years from onset of exposure should be considered. This is discussed in Chapter 6.

The above discussion supports a general model for lung cancer in which the asbestos-related risk, t years from onset of exposure, is proportional to the cumulative exposure to asbestos at time t-10 years multiplied by the age

and the calendar year risk of lung cancer in the absence of exposure. The incidence of lung cancer can be expressed formally by

$$I_L(a,y,t,d,f) = I_E(a,y)\ [1 + K_L \cdot f \cdot d(t-10)] \qquad (3\text{-}3a)$$

Here, $I_L(a,y,t,d,f)$ is the lung cancer incidence observed or projected in a population of age, a, observed in calendar period, y, at t years from onset of an asbestos exposure of duration, d, and average intensity, f. $I_E(a,y)$ is the age and calendar year lung cancer incidence expected in the absence of exposure. If smoking data are available, I_L and I_E can be smoking-specific incidences. f is the intensity of asbestos exposure to fibers longer than 5 μm/ml (f/ml), d is the duration of exposure up to 10 years from observation, and K_L is a proportionality constant that is a measure of the carcinogenic potency of the asbestos exposure. A delay in manifestation of risk is based on the data of Seidman (1984) and Selikoff et al. (1979); in neither study was any excess lung cancer seen prior to 10 years from onset of exposure. From Equation 3-3a, the relative risk of lung cancer, I_L/I_E, is independent of age and depends only on the cumulative exposure to asbestos.

Different asbestos varieties have different size distributions, and the fraction greater than 5 μm depends on fiber type and the production process (Nicholson et al., 1972; Gibbs and Hwang, 1975). Animal data demonstrate that dimensions (length and width) are important variables in fiber carcinogenicity. Thus, K_L would be expected to depend on fiber type and fiber dimension. In practice, however, uncertainties in establishing quantitative dose-response relations, through the application of Equation 3-3a to observed data, may preclude the determination of K_L by fiber type (see Section 3.17).

3.7 MULTIPLE FACTOR INTERACTION WITH CIGARETTE SMOKING

The multiplicative interaction between asbestos and the underlying risk of lung cancer is seen in the synergism between cigarette smoking and asbestos exposure, first identified by Selikoff et al. (1968). Later data on U.S. insulation workers confirm and extend the initial findings (Hammond et al., 1979a): In this larger study, 12,051 asbestos workers, 20 or more years from onset of their exposure, were followed from 1967 through 1976. At the outset, 6841 volunteered a history of cigarette smoking, 1379 said they had not smoked

cigarettes, and the rest provided no information. By January 1, 1977, 299 deaths had occurred among the cigarette smokers and 8 among those not reported as smokers.

This experience was compared to an age- and calendar year-specific basis with that of like men with the same smoking habits in the American Cancer Society's prospective Cancer Prevention Study (Hammond, 1966). For the control group, 73,763 white males who were exposed to dusts, fumes, gases, or chemicals at non-farming work were selected. The age standardized rates per 100,000 person-years for each group are shown in Table 3-9. The results show that both the smoking and non-smoking lung cancer risks are multiplied five times by the worker's asbestos exposure. However, since the risk is low for non-smokers, multiplying it five times does not result in many cases, although any excess is clearly undesirable. On the other hand, smoking by itself causes a major increase and when that high risk is then multiplied five times, an immense increase is found. Corroborative data on the multiplicative smoking-asbestos interaction are seen in studies by Berry et al. (1972), McDonald et al. (1980), and Selikoff et al. (1980). However, these do not show as exact a multiplicative effect as that of Hammond et al. (1979a).

TABLE 3-9. AGE-STANDARDIZED LUNG CANCER DEATH RATES FOR CIGARETTE SMOKING AND/OR OCCUPATIONAL EXPOSURE TO ASBESTOS DUST COMPARED WITH NO SMOKING AND NO OCCUPATIONAL EXPOSURE TO ASBESTOS DUST

Group	Exposure to asbestos?	History cigarette smoking?	Death rate[a]	Mortality difference	Mortality ratio
Control	No	No	11.3	0.0	1.00
Asbestos Workers	Yes	No	58.4	+47.1	5.17
Control	No	Yes	122.6	+111.3	10.85
Asbestos Workers	Yes	Yes	601.6	+590.3	53.24

[a]Rate per 100,000 person-years standardized for age on the distribution of the person-years of all the asbestos workers. Number of lung cancer deaths based on death certificate information.

Source: Hammond et al. (1979a).

The study by Hammond et al. (1979a) also carried the asbestos-smoking interaction a step further, to show increased risk of death from asbestosis. As noted previously, insulation work carries a risk of fatal progressive pulmonary fibrosis, and some of those who never smoked cigarettes died of asbestosis. Nevertheless, asbestosis mortality for men who smoked a pack or more a day was 2.8 times higher than for men who never smoked regularly. Cigarette smoking, with resulting bronchitis and emphysema, adds an undesirable and sometimes unsupportable burden to the asbestos-induced pneumoconiosis. Interactive effects between cigarette smoking and the prevalence of X-ray abnormalities were reported previously (Weiss, 1971). However, no relationship was found in the Hammond et al. (1979a) study (Seidman, quoted in Frank, 1979) between cigarette smoking and the risk of death from mesothelioma or gastrointestinal cancer.

3.8 METHODOLOGICAL LIMITATIONS IN ESTABLISHING DOSE-RESPONSE RELATIONSHIPS

There are substantial difficulties in establishing dose-response relationships for human exposure to asbestos, perhaps the most important being that current health effects are the result of exposures to dust in previous decades when few and imperfect measurements of fiber concentrations were made. Current estimates of what such concentrations might have been can be inaccurate, since individual exposures were highly variable. Further, while disease response now can be established through epidemiological studies, these, too, can be misleading because of methodological limitations. Despite this difficulty, useful estimates of risk can be made to provide an approximate measure of asbestos disease potential in environmental circumstances. Limitations of existing data can be taken into account and their recognition can stimulate appropriate research to fill identified gaps.

One of the important limits on the accuracy of exposure-response data for asbestos diseases is our lack of information concerning past fiber exposures of those populations whose mortality or morbidity have been evaluated. Few measurements were made in facilities using asbestos fibers prior to 1965, and those measurements that were done quantified all dust (both fibers and particles) present in the workplace air. Current techniques, using membrane filters and phase contrast microscopy for the enumeration of fibers longer than 5 μm, have been utilized in Great Britain and the United States only since 1964 (Ayer et

al., 1965; Holmes, 1965). They have been standardized in the United States only since 1972 (National Institute for Occupational Safety and Health, 1972; Leidel et al., 1979), and even later in Great Britain.

Modern counting techniques may be utilized to evaluate work practices and ventilation conditions believed to be typical of earlier activities. However, it is always difficult to duplicate materials and conditions of earlier decades so that such retrospective estimates are necessarily uncertain. Alternatively, fiber counting techniques using the particle counting instrumentation of earlier years can be used now to evaluate a variety of asbestos-containing aerosols. The comparative readings would then serve as a "calibration" of the historic instrument in terms of fiber concentrations. Unfortunately, the calibration depends on the type and size distribution of the asbestos used in the process under evaluation and on the quantity of other dust present in the aerosol. Thus, no universal conversion has been found between earlier dust measurements and current fiber counts.

In the United States and Canada, those few data that were obtained on asbestos workers' exposures prior to 1965 are based largely upon total dust concentrations measured using a midget impinger. Fibers were inefficiently counted with this instrument because of the use of bright field microscopy. Attempts to compare fiber concentrations with midget impinger particle counts generally showed poor correlations (Ayer et al., 1965; Gibbs and LaChance, 1974) (e.g., see Figure 3-6). In the United Kingdom, the thermal precipitator was used from 1951 through 1964 in one plant for which environmental data have been published. This instrument, too, does not allow accurate evaluation of fiber concentrations. The variability in the correlation between fiber measurements and thermal precipitator data is reported to be large (Steel, 1979), but no specific data are given. Finally, both the midget impinger and the konimeter were often used as area rather than personal samplers. Sources of dust were often sampled for control purposes, even though no personnel were directly exposed.

Even with the advances in fiber counting techniques, significant errors may be introduced into attempts to formulate general fiber exposure-response relationships. The convention now in use, that only fibers longer than 5 μm be counted, was chosen solely for the convenience of optical microscopic evaluation (since surveillance agencies are generally limited to such instrumentation). It does not necessarily correspond to any sharp demarcation of effect for asbestosis, lung cancer, or mesothelioma. While it is readily

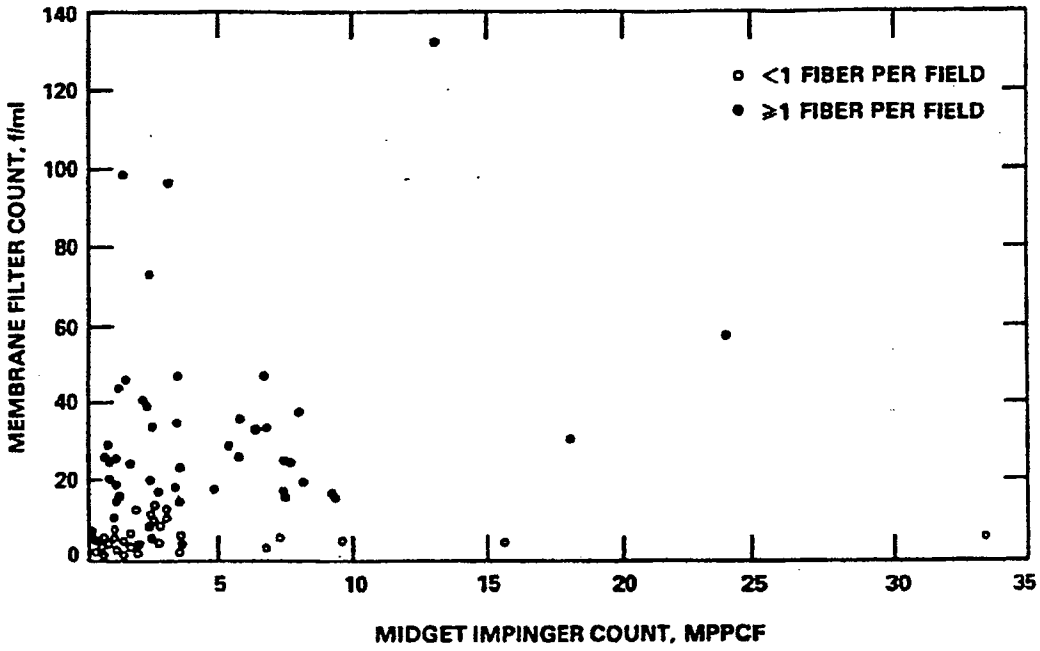

Figure 3-6. A plot of membrane filter and midget impinger counts; MPPCF represents millions of particles per cubic foot.

Source: Gibbs and LaChance (1974).

understood that counting only fibers longer than 5 μm enumerates just a fraction of the total number of fibers present, there is incomplete awareness that the fraction counted is highly variable, depending upon the fiber type, the process or products used, and even the past history of the asbestos material (e.g., old versus new insulation material), among other factors. For example, the fraction of chrysotile fibers longer than 5 μm in an aerosol can vary by a factor of 10 (from as little as 0.5 percent of the total number to more than 5 percent). When amosite aerosols are counted, the fraction longer than 5 μm may be 30 percent, extending the variability of the fraction counted to two orders of magnitude (Nicholson et al., 1972; Nicholson, 1976a; Winer and Cossette, 1979).

Even if consideration is restricted to fibers longer than 5 μm, many fibers are missed by optical microscopy. Using electron microscopy, Rendall and Skikne (1980) measured the percentage of fibers with a diameter less than 0.4 μm (the approximate limit of resolution of an optical microscope) in various asbestos dust samples. In general, they found that more than 50 percent of the 5 μm or longer fibers are less than 0.4 μm in diameter and, thus, are not visible using a standard phase contrast optical microscope. Moreover, as with length distribution, diameter distribution varies with activity and fiber type. As a result, the fraction of fibers longer than 5 μm visible by light microscopy varies from about 22 percent in chrysotile and crocidolite mining and amosite/chrysotile insulation manufacturing to 53 percent in amosite mining. Intermediate values of 40 percent are measured in chrysotile brake lining manufacturing and 33 percent in amosite mill operations. Thus, even perfect measurement of workplace air, with accurate enumeration of fibers according to currently accepted methods, would be expected to lead to different exposure-response relationships for any specific asbestos disease when different work environments are studied. Conversely, risks estimated for a given exposure circumstance must have a large range of uncertainty to allow for the variability resulting from fiber size effects.

Those uncertainties in the physical determinations of past fiber concentrations and the difficulty in evaluating the exposure parameter of importance in current measurements are exacerbated by sampling limitations in determining individual or even average exposures of working populations; only few workmen at a worksite are monitored, and then only occasionally. Variability in work practices, ventilation controls, use of protective equipment, personal habits,

and sampling circumstances add considerable uncertainty to our knowledge of exposure.

Statistical variability associated with small numbers and methodological difficulties in the estimation of disease also are important contributions to the variability in exposure-response relationships. Studies can be significantly biased by inclusion of recently employed workers in study cohorts, use of short follow-up periods, and improper treatment of the various time factors that are important in defining asbestos cancer. Particularly, inadequacies of tracing, can lead to significant misestimates of disease. Generally, 10 percent to 30 percent of an observation cohort will be deceased (sometimes even less). If 10 percent of the group is untraced and most are deceased, very large errors in the determination of mortality could result, even if no person-years are attributed to the lost-to-follow-up group. Finally, the choice of comparison mortality rates can introduce substantial errors. Local rates are generally the most desirable to use, but these may be unstable because of small numbers, or they may be affected by special circumstances (e.g., other industry). Data on general population worker mortality rates are not available, and existing general population rates may overstate the expected total mortality due to a "healthy worker effect" (Fox and Collier, 1976). Proper consideration of smoking habits is important in the determination of lung cancer risks. Unfortunately, full information on the smoking patterns of all individuals in a cohort is often not available.

3.9 QUANTITATIVE DOSE-RESPONSE RELATIONSHIPS FOR LUNG CANCER

In concept, exposure-response relationships can best be determined from studies in which individual exposures are estimated for each cohort member, subgroups are established according to cumulative exposure (with proper consideration of time factors), and an exposure-response relationship is determined from effects observed in all exposure categories. Consistencies in the observed exposure-response relationships, and an appropriate intercept at zero exposure, strengthen the risk estimates made from such studies. Dose-response relationships are commonly obtained by two methods. One method utilizes mortality rates in a comparison population (usually the general population of the same area) with standard mortality ratio (SMR) calculated for each exposed subgroup by multiplying the ratio of observed to expected deaths by 100. Crucial to the validity of the calculation is the choice of comparison rates.

Ideally, exposures to confounding factors, such as from cigarettes, should be the same in the study and comparison populations. The second method generates a relative risk (RR) factor at each exposure by a case-control anaylsis, where the number of cause-specific deaths is compared with the number of internal controls in each dose category. Such analysis is less subject to confounding factors in the comparison population, but has greater statistical variability.

In calculating a dose-response relationship, a weighted, rather than unweighted, least square analysis is most appropriate because there are large differences in the statistical validity of the individual SMRs or RRs in a given study. Values of K_L, the fractional increase in risk per unit exposure, can be calculated directly from the slopes of the regression lines of SMR or RR on dose (with a conversion, if necessary, from mppcf-y to f-y/ml).

Ideally, regression lines should pass through zero dose at an SMR of 100 or an RR of 1. The chances of this occurring are minimal. Statistical variability, even in the most ideal circumstances, will lead to intercepts different from that expected; in the case of SMRs, the comparison population may not be completely appropriate; incomplete tracing of a cohort can distort both SMRs and RRs; the comparison group in a relative risk analysis usually has some exposure; and finally, dose-response relationships can be affected by improper estimates of dose. It is important to identify the factor which may have led to an abnormal intercept, because it would indicate what adjustments might be made to the observed slope. For example, if improper comparison rates were used for the calculation of SMRs, and they were the sole cause of a higher or lower than expected intercept, it would be appropriate to divide both the slope and the intercept by the intercept/100 because the same percentage misestimate would be expected to exist in each exposure category. However, if the deviation from 100 were simply random, such division would compound what is already a statistical misestimate of the true slope. For example, if statistical variability led to an SMR intercept higher than 100, the observed slope would be less than the true slope. To divide by the intercept/100 would reduce it even further.

It may be difficult to identify misestimates of dose, especially within a single study. However, comparisons between estimates in similar exposure circumstances by different groups are useful in establishing the reasonableness of stated exposure estimates. In analyses of the available data on lung cancer risk for several studies, the uncertainties associated with response are

greater than those associated with dose. This is particularly true in groups demonstrating low risks, where the difference between observed and expected deaths has an extremely large uncertainty relative to the difference.

Dose-response data can also be obtained using the overall SMR for a group and the average exposure for all cohort members. This calculation assumes that a linear dose-response relationship exists throughout the range of exposure and that the comparison population rates are appropriate to the study population. The first assumption would appear to be generally valid for lung cancer, but the second must be considered carefully in the analysis of each study. Such calculations will generally use Equation 3-3a, which is simplified as

$$I_L = I_E(1 + K_L \cdot f \cdot d) \qquad (3\text{-}3b)$$

Rearranging, one obtains

$$K_L = [(I_L - I_E)/I_E]/f \cdot d \qquad (3\text{-}3c)$$

or

$$K_L = [(I_L/I_E) - 1]/f \cdot d \qquad (3\text{-}3d)$$

$$= (\text{Relative Risk} - 1)/\text{Cumulative Exposure}$$

Two approaches are possible in developing an exposure-response relationship for asbestos. One is to select the study or studies with the best exposure data, assuming an adequate measure of effect. The exposure-response relationship developed certainly would apply to similar exposure circumstances and may apply to others as well. Alternatively, all studies for which exposure-response information is available can be utilized along with estimates of the uncertainty of such data. An appropriate weighted average of the relationships found in different studies, taking into account observable differences in exposure circumstances, yields an overall exposure-response relationship. The former procedure has particular merit in evaluating the risk from an agent whose exposure can be well characterized, such as that from a single chemical species. However, this is not the case with asbestos where we are generally concerned with exposures to mixtures of different asbestos minerals. Even exposures to a single mineral species can involve substantially different fiber-size distributions which would strongly affect the carcinogenic potentials of the exposures. As mentioned above, a large fraction (usually greater than 50 percent)

of the fibers longer than 5 μm are too thin to be visible by light microscopy. These thin and long fibers are the most carcinogenic in experimental studies (see Chapter 4) and are believed to be so in humans. The fraction of these uncounted fibers will vary with the particular process and a study or studies selected on the basis of the "best exposure measurements" may not be typical of most exposure circumstances in terms of its fiber-size distribution, even for one asbestos mineral. Thus, the quality of "good" exposure data for carcinogenic risk assessment may be illusionary.

The advantages of considering all studies for which exposure-response data can be developed are

1. any bias in the choice of studies selected for analysis is largely removed,
2. information can be obtained on the uncertainty of the estimate of an average value of K_L,
3. estimates of the effect of fiber type differences or process differences can be estimated better. Such information is of crucial importance and efforts to obtain it are warranted.

Primary among the disadvantages of the use of all exposure-response data is the fact that the quality of some of the data can only be estimated subjectively. The statistical variability in measures of response can be established quantitatively. However, biases in epidemiological studies may not be perceived and, of most importance, evaluations of the quality of exposure estimates are highly subjective, as are the estimates themselves.

Because of the above advantages, in the analysis that follows, all studies that provide exposure-response information are utilized. This procedure was also followed in the asbestos health effects reviews of the Consumer Products Safety Commission (1983) and the National Academy of Sciences (1983). In contrast, the recently published review by Doll and Peto (1985) for the British Health and Safety Commission selected two studies for analysis, based upon the quality of exposure measurements. These were the study by McDonald et al. (1983) of South Carolina textile workers and Peto et al.'s (1985) update of the mortality of Rochdale textile workers. As will be seen, their results are virtually identical to those obtained using all available studies.

In this document estimates of K_L are made from all sources of data within each study. If the data indicate that the results of a study are substantially

affected by possible misestimates of exposure, that non-local rates are used for the expected mortality, or that inadequate tracing exists, an adjustment and its magnitude are clearly indicated. Consideration is made for deviations of the intercept of SMR regression lines from 100. However, if the source of the deviation cannot be identified, the slope as calculated is used.

For nine studies, values of K_L are estimated from a weighted linear regression analysis of the relationship between lung cancer risk and cumulative exposure. The weighting is the reciprocal of the variance of a particular data point. Perceived biases are taken into account and adjustments for them described in the text. Generally, the adjustment accounts for the difference in local lung cancer rates compared to those used in the published study. A value for K_L is calculated for each study using the slope of observed dose-response data, the slope of the odds ratios at different doses in case control analyses, or an average of the two procedures when both are done. In three studies, K_L is estimated from the difference in risk between heavily and lightly exposed groups (using individual exposure estimates) and/or the risk estimated from the ratio of overall excess lung cancer to the average exposure for the group. Finally, in one study, the relationship between SMR and duration of employment is used, assuming average group exposure per year of employment.

Table 3-10 shows the results of a variety of analytical procedures using the published data in 14 studies, along with 95 percent confidence limits calculated from the variance of the observed number of lung cancer cases and the slope of weighted regression lines. Adjustments for potential biases are shown as well as alternate regression analysis which either forces the regression line through an SMR of 100 at 0 dose or adjusts for a non-zero intercept by dividing by the intercept/100. It is emphasized that these two procedures can lead to misestimates of the actual exposure and increased uncertainty estimates. They are included, however, to provide a measure of the uncertainty that may be associated with regression analysis. Further, an analysis is shown in which the overall SMR and average exposure of the group was utilized to estimate the value of K_L. This analysis is particularly useful in estimating the range of uncertainty that may be present in given studies. For example, consider the study of Peto (1980). In the cohort exposed after 1950, 11 lung cancers were observed and 3.35 expected in the group followed 15 years after first employment and deemed to have a cumulative exposure of 200 f-y/ml. The

excess risk is 7.65 cases, using Equation 3-3c, and K_L = (11 - 3.35)/3.35/200 = 0.0114 $(f\text{-}y/ml)^{-1}$. Assuming the number of deaths is an expression of a Poisson variate, the 95 percent confidence limit (from statistical considerations) will be from K_L = [0.0114 (5.4 - 3.35)]/7.75 to K_L = [0.0114 (19.7 - 3.35)]/7.75; i.e., from 0.0030 to 0.024.

The method for estimating K_L and the 95 percent confidence limit for each study is described in the text that follows. These data are listed in Table 3-10 and displayed in Figure 3-7. In addition to the statistical uncertainty listed in Table 3-10, the effect of a ± two-fold range of uncertainty in cumulative exposure is indicated in Figure 3-7 for most studies. This twofold range is a subjective choice, but is felt to be a realistic representation of the uncertainty in the cumulative exposure estimates from all the sampling problems mentioned previously. In some cases, for specific reasons listed, a greater exposure uncertainty is indicated. Even though response uncertainties and exposure uncertainties are unlikely to be correlated, the overall 95 percent confidence limit on a study is considered to be the sum of the listed exposure and response uncertainties.

3.9.1 Textile Products Manufacturing, United States (Chrysotile); Dement et al. (1982, 1983a, 1983b)

Mortality data from a chrysotile textile plant studied by Dement et al. (1982, 1983a, 1983b) allow a direct estimate of lung cancer risk per fiber exposure. Here, data from impinger measurements of total dust in terms of mppcf were available, characterizing dust concentrations since 1930. Further, 1106 paired and concurrent impinger-membrane filter measurements allow conversion of earlier dust measurements to fiber concentrations, suggesting that 3 f/ml is equivalent to 1 mppcf for all operations except fiber preparation. (The 95 percent confidence interval is 2-3.5 f/ml/mppcf.) A value of 8 f/ml/mppcf characterizes fiber preparation work (confidence interval, 5-9). Subsequent to 1940, average fiber concentrations in most operations are estimated to range from 5 to 10 f/ml, with the exception of fiber preparation and waste recovery where mean concentrations are 10-80 f/ml.

The study cohort consisted of all 1261 white males employed one or more months between January 1, 1940 and December 31, 1965. Vital status was determined for all but 26 individuals who were considered alive for purposes of analysis. SMRs for lung cancer were presented for five exposure categories in terms of cumulative fiber exposure (Table 3-11). A weighted regression line

TABLE 3-10. ESTIMATES OF THE PERCENTAGE INCREASE IN LUNG CANCER PER f-y/ml OF EXPOSURE (100 x K_L), ACCORDING TO DIFFERENT PROCEDURES IN 14 EPIDEMIOLOGICAL STUDIES

Study	Years from onset	Directly from weighted SMR regression	Adjusted for local rates or other factors (see text)	Adjusted to SMR = 100 at zero dose	SMR regression forced through 100 at zero dose	RR regression adjusted to RR = 1 at zero dose	Overall SMR-100 divided by average exposure	Adjusted for local rates or other factors (see text)	Adopted values and range
Dement et al., 1983b	15	4.19(±1.65)[a]	2.79(±1.10)	2.77(±1.08)	4.48(±1.10)		5.37 (2.94-8.45)	3.58 (1.99-5.63)	2.8 (1.7-5.6)
McDonald et al., 1983a	20	2.07(±0.90)	1.38(±0.33)	1.88(±0.45)	2.21(±0.39)	3.72(±2.04)	3.22 (1.46-4.95)	2.15 (0.97-3.30)	2.5 (1.0-3.7)
Peto, 1980	15						1.14 (0.30-2.41)		1.1 (0.30-2.4)[b]
McDonald et al., 1983b	20	0.86(±0.29)	1.06(±0.35)	1.62(±0.55)	0.41(±0.71)	1.71(±0.93)	0.10 (0.0-0.66) 0.87 (0.29-1.79)[c]	0.12 (0.0-0.81) 1.07 (0.36-2.21)	1.4 (0.36-1.7)
Berry & Newhouse, 1983	10					Negative	0.068 (0.0-0.52)		0.058 (0.010-0.80)
McDonald et al., 1984	20	Negative			0.13(±1.63)	0.003(±0.95)	0.79 (0.017-1.74) 0.085 (0.0-0.55)[d]		0.010 (0.010-0.55)
McDonald et al., 1980	20	0.043(±0.015)	0.064(±0.022)	0.047(±0.016)	0.035(±0.014)	0.057(±0.009)	0.045 (0.016-0.074)	0.064 (0.023-0.11	0.060 (0.023-0.11)
Nicholson et al., 1979	20	0.23(--)[e]	0.30(--)		0.30(--)		0.011 (0.043-0.21)	0.17 (0.064-0.32)	0.17 (0.064-0.32)
Rubino et al., 1979	20	0.51(--)[e]				0.89 (--)	0.013 (0.0-0.36)		0.075 (0.010-0.89)
Seidman, 1984	5	2.72(±1.06)		0.84(±0.33)	4.28(±2.27)		5.92 (4.49-7.36)		4.3 (0.84-7.4)
Selikoff et al., 1979	20	1.10(±0.097)	0.75(±0.066)				0.86 (0.75-0.97)	0.69 (0.60-0.78)	0.75 (0.60-1.1)
Henderson & Enterline, 1979	ret.[f]	0.34(±0.17)	0.49(±0.25)	0.24(±0.12)	0.43(±0.13)		0.046 (0.27-0.63)	0.67 (0.39-0.91)	0.49 (0.24-0.91)
Weill et al., 1979	20	0.31(±0.31)	0.53(±0.54)	0.42(±0.44)	0.22(±0.31)	0.35(±0.26)	0.041 (0.0-0.36) 0.034 (0.13-0.63)[g]	0.64 (0.0-1.1) 0.38 (0.14-0.70)	0.53 (0.14-1.1)
Finkelstein, 1983	20	Negative				4.80(±5.29)	6.70 (3.53-11.25)		6.7 (3.5-11.2)

[a] () = 95% confidence limits.

[b] Doll and Peto (1985) refer to an update of this study (Peto et al. 1985). They calculate values of 1.5 and 0.54 for 100 x K_L for workers first exposed after 1950 and after 1932, respectively.

[c] Calculated from highest exposure category.

[d] Calculated omitting lowest exposure category.

[e] Only two values.

[f] Retirees.

[g] Calculated from highest two exposure categories.

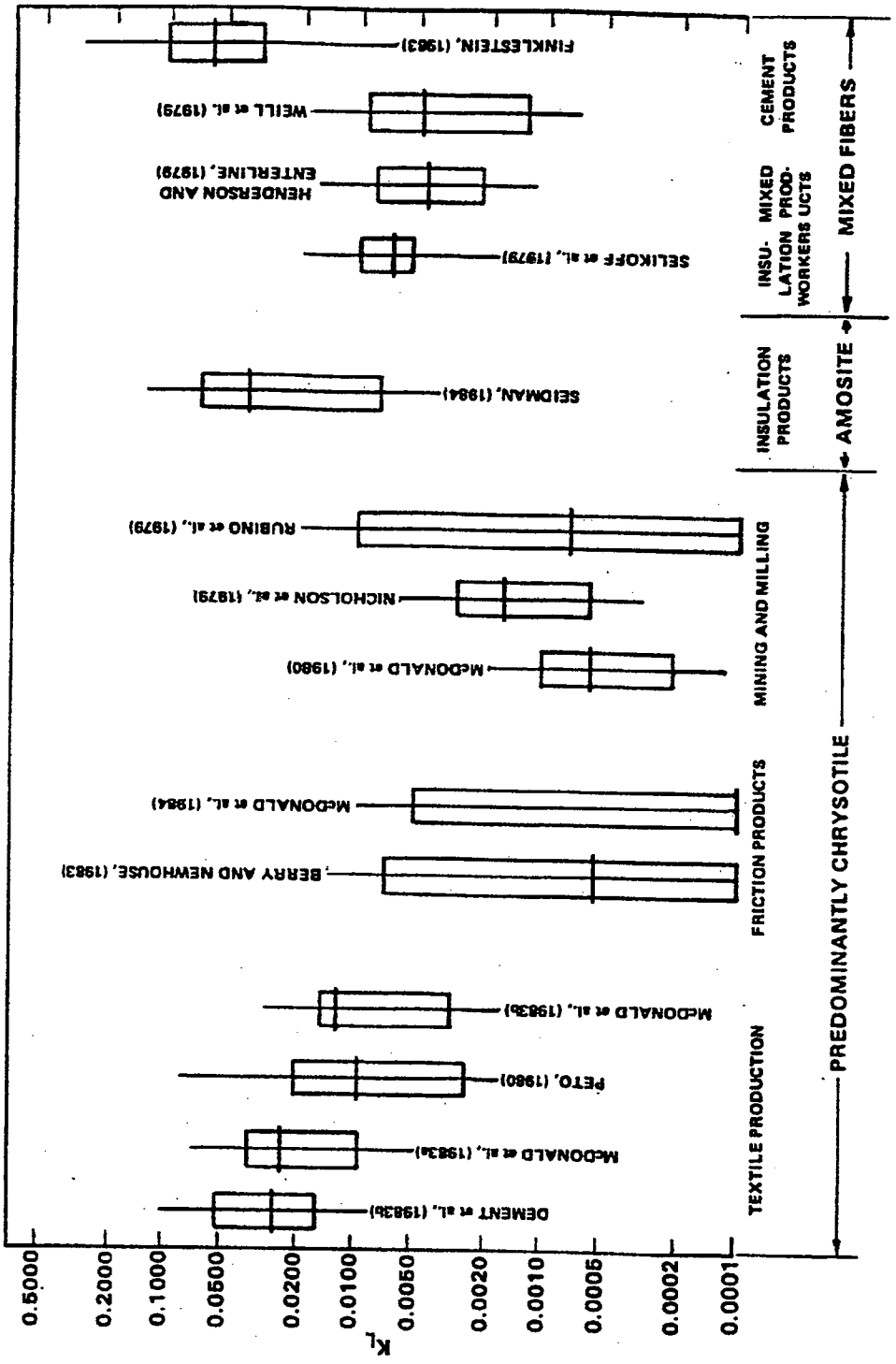

Figure 3-7. Values of K_L, the fractional increase in lung cancer per f-y/ml of exposure in 14 asbestos exposed cohorts. The open bar reflects the estimated 95% confidence limits associated with measures of response. The line represents the uncertainties associated with measures of exposure, generally ± a factor of two.

TABLE 3-11. LUNG CANCER RISKS, BY DOSE, AMONG SOUTH CAROLINA ASBESTOS TEXTILE WORKERS (Dement et al., 1983b)

Exposure in f-y/ml	SMR
1.4 (<2.74)	140 (5)[a]
15.1 (2.74-27.4)	279 (9)
68.5 (27.4-109.6)	352 (7)
191.8 (109.6-274.0)	1099 (10)
411.0 (>274.0)	1818 (2)
Complete cohort:	336 (33)

Estimated average cumulative exposure: 43.9 f-y/ml

[a]( ) = number of deaths.

Regression equations

SMR = 150 + 4.19(±0.84) x f-y/ml weighted
SMR = 169 + 4.13(±0.32) x f-y/ml unweighted

Weighted regression equation forced through an SMR of 100
SMR = 100 + 4.48(±0.56) x f-y/ml

yields SMR = 150 + 4.19 x f-y/ml, for a K_L of 0.042. The standard error of the estimate of the slope is ± 0.84.

Dement et al. (1983b) uses U.S. rates for calculating expected deaths. Age-adjusted county rates are 75 percent higher, i.e $66.5/10^5$ versus $38.0/10^5$ (Mason and McKay, 1974). Dement et al. presents arguments for using national rates. Local rates are probably influenced by nearby shipyard employment (and perhaps by the study plant) and the smoking habits of the study population reflect those of the U.S. general population. Blot et al. (1979) found that World War II shipyard employment leads to a 60 percent increased risk of lung cancer. This increase, however, would be substantially diluted in county rates. Across the United States these rates are 11 percent higher in shipyard counties compared with control counties. Further, Acheson and Gardner (1983) point out that the rates for women in the county are equally high and they suggested an exposure to some unknown carcinogen in the population. The age-adjusted rates of contiguous counties are only 16 percent greater than

those of the United States; those of the State of South Carolina are virtually identical to the United States rates.

It is unlikely that the origin of the high local rates will ever be resolved. As seen above, the SMR at zero exposure is calculated to be 150 from the weighted regression analysis. We will use this value as a measure of possible overestimates of the SMRs at all exposures, and we will divide the value of K_L above by 1.5. This brings the SMR at zero exposure to 100 and allows virtually full consideration that higher local rates are the appropriate comparison. (The remainder would be accounted for by shipyard employment.) The adjusted K_L is 0.028.

3.9.2 Textile Products Manufacturing, United States (Chrysotile); McDonald et al. (1983a)

Exposure-related mortality data at this same plant have recently been published by McDonald et al. (1983a). Their cohort consisted of all individuals employed for one or more months prior to January 1, 1959 and for whom a Social Security Administration (SSA) record existed. This eliminated from consideration individuals who began and ended their employment prior to mid-1937, when SSA numbers were first assigned. The same data used by Dement on past exposures were utilized to assign cumulative dust exposures, in mppcf-y, to each study participant. Male deaths, by cause, 20 years after first employment, are related to dust exposure accumulated to 10 years prior to death. Data for lung cancer are shown in Table 3-12. A weighted regression analysis yields the relation SMR = 110 + 6.22 mppcf-y. No data are given by McDonald et al. (1983a) on cumulative fiber exposures. If we use the average relationship found by Dement et al., 1 mppcf = 3 f/ml, we obtain a K_L of 0.021. Adjusting by the value 1.5, as above, to account for the higher local rates, yields a K_L of 0.014. (McDonald et al. (1983a) used South Carolina rates rather than local rates).

McDonald et al. (1983a) also made estimates of risk using a Mantel and Haenszel (1959) case-control analysis, as in Table 3-12. A weighted regression line yields a slope of 0.068. Because the RR regression was obtained using internal controls, no adjustment for local rates is necessary. However, since the controls were exposed, the zero dose intercept should be used as the measure of risk in an unexposed group. This requires dividing the slope by the intercept to obtain an adjusted regression line. Dividing by the zero exposure intercept, 0.61, and by 3 to convert to fiber exposures, gives a